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Risk Factors for Hepatocellular Carcinoma and Its Mortality Rate: A Multicenter Study in Indonesia

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Abstract

Background: Hepatocellular carcinoma (HCC) is a rising cause of mortality and a significant burden. Therefore, a population-based cancer registry is an essential element to provide a baseline and comprehensive analysis of the patient's risk factors. We present a multicentre HCC registry at two hospitals in Indonesia.

Methods: We performed a follow up on HCC patients admitted between January 2015 and November 2017 in Cipto Mangunkusumo National General Hospital and Dharmais Hospital, Jakarta, Indonesia. The primary outcome was the patient's death which also was the endpoint of the follow up evaluation. We conducted a multivariate analysis using logistic regression and calculated the odds ratio (OR) with 95% confidence intervals (CIs).

Results: In this study, there were 282 HCC patients and the mean age was 55 ± 12.75 years. As many as 74.8% (211/282) patients were male and hepatitis B virus (HBV) was the most common etiology found (63.1%; 178/282). At the last follow up, 136 (48.2%) patients have died. Mortality rate was not significantly affected by the patient's sex, age, hepatitis etiology, cirrhotic status, nor HCC surveillance. Based on Child-Pugh (CP) classification, the odds increase progressively in CP C patients (OR 1.95; 95% CI 1.08-3.53; p=0.026). The progressive increase was also found in higher Barcelona Clinic Liver Cancer (BCLC) stage of HCC with odds ratio for C and D patients were 3.50 (95% CI 1.18-10.38; p=0.024) and 3.41 (95% CI 1.02-11.41; p=0.047) respectively. Supportive treatment was the most dominant treatment modality with odds ratio 2.17 (95% CI 1.14-4.16; p =0.019) and was found to be associated with HCC mortality rate. The median survival of all patients was 17 months from the date of diagnosis.

Conclusion: Child-Pugh classification, BCLC stage and treatment modality might predict mortality in HCC patients. Other parameters need further evaluation.

Keywords: Hepatocellular carcinoma; Cirrhosis; Mortality; Risk factors

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide. It is the most common primary liver cancer with very poor prognosis and outcome. The incidence is much higher in men and stands as third most common cancer among men and seventh in women. Eastern and South-Eastern Asia have the highest incidence with the age-standardized ratio (ASR) of 31.9 and 22.2 per 100.000 respectively [1]. A study in Indonesia by Mulyana investigated that HCC patients' survival in Cipto Mangunkusumo National General Hospital was very low with only 4.8 months of median survival and 24.1% one-year survival rate. After fifteen years, a recent study in Indonesia showed no improvement in the survival of HCC patients with 29.4% one-year survival rate [2]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the primary cause of HCC, while hepatitis B is more common in Asia and developing countries [3]. Moreover, the endemicity of hepatitis B in Indonesia is intermediate to high and varied between region ranging from 4.7 to 11.2% [4].

Lack of physician awareness and risk factors screening program in our population might contribute to the low level of HCC surveillance. This leads to an increasing number of HCC mortality despite its considerable preventive measures, screening tools, and treatment modalities. Therefore, we present a population-based cancer registry to provide physicians and health practitioners a baseline data for HCC patient management.

Methods

Study design and population

We conducted a cohort retrospective data study from two tertiary hospitals (Cipto Mangunkusumo National General Hospital and Dharmais Hospital) between January 2015 to November 2017. There were 282 HCC patients recruited in this study (158 patients from Cipto Mangunkusumo National General Hospital and 124 patients from Dharmais Hospital). The inclusion criterion was a confirmed HCC diagnosis, while patients with other malignancy and incomplete laboratory or clinical data were excluded.

Data collection

Baseline clinical data was collected at the time of diagnosis. Diagnosis of HCC was confirmed by biopsy and radiology. The specific finding from CT-scan or MRI is hypervascular in arterial phase and washout in venous and delayed phase. From biopsy, we can find a liver cell differentiation and accompanied by tumor tissue stroma consisting of sinusoid-like blood space lined by a layer of endothelial cells. There was no non-liver metastatic incidence observed. Patients were grouped by whether they were diagnosed from routine surveillance or detected from their symptoms. Information on patients' gender, age, hepatitis marker, laboratory data of liver function (albumin, bilirubin, AST, ALT), and clinical conditions (ascites, encephalopathy, the appearance of cirrhosis and portal vein thrombus) were collected. Child Turcotte Pugh (CP) score was calculated from albumin, bilirubin, international normalized ratio (INR), ascites, and encephalopathy and then classified into three following classes: 5-6 score for CP A, 7-9 score for CP B, 10-15 score for CP C. Staging was done using Barcelona Clinical Liver Cancer (BCLC) staging system [5].

Patients were also separated into three groups based on their treatment modality: curative, palliative, and supportive. The curative protocol consisted of surgical resection and radiofrequency ablation (RFA). The palliative protocol consisted of radiation therapy, transarterial chemo-embolization (TACE), and transarterial chemo-infusion (TACI), sorafenib. Meanwhile, the supportive protocol provided patients with best supportive care therapy.

Patients' death was investigated from their medical records or through contacting the families by phone. If the phone number could not be contacted, the medical team follows up by visiting their home address, providing an assignment letter from the hepatobiliary division.

Statistical analysis

The analysis was performed using IBM SPSS statistics 23.0. Continuous data was shown with the mean (SD) or median (minimum-maximum), depending on the result of the normality test. Categorical data were expressed as frequency (percentage). Kaplan Meier was used to calculate mortality and significance parameter for risk HCC mortality identified with log rank test. Multivariate analyses performed by using Cox Proportional Hazard Regression. Variables with p value under 0.25 were included as model regression. Statistical significance was defined by P value under 0.05. The magnitude of the association between risk factors and mortality was explained by odds ratio (OR) with 95% confidence intervals (CIs).

Ethics

This study was approved by the Ethics Committee of The Faculty of Medicine, University of Indonesia.

Results

Characteristics of the study population were listed in **Table 1**. A total of 282 patients with HCC were included in this study. Among them, 158 patients were from Cipto Mangunkusumo National General Hospital and 124 patients were from Dharmais Hospital. Hepatocellular carcinoma occurred more frequent in male patients. The mean age at the time of diagnosis was 55 ± 12.75 years. The number of hepatitis B patients accounted for more than half of the study population and became the most common etiology. The rest of etiologies were hepatitis C, non-B non-C, and co-infection of hepatitis B and hepatitis C. Mean albumin of the patients was 3.5 0.83 g/dL and median (range) total bilirubin was 1.20 (0.23-34.58) mg/dL. A slight increase was found in liver function test with median (range) AST was 87 (1-1,613) U/L and median (range) ALT was 46 (3-1,331) U/L.

From the entire group, most patients were classified as CP A, followed by CP B and CP C. However, half of the patients in Cipto Mangunkusumo National General Hospital had CP A, while CP B was more commonly found in Dharmais Hospital. Cirrhosis was detected in 58.2% patients and only 6% of HCC patients were detected during routine surveillance. Most of them (94%) were diagnosed with HCC from the appearance of their clinical symptoms. In Cipto Mangunkusumo National General Hospital, BCLC stage B was the most common stage of HCC, while BCLC stage C was more common in Dharmais Hospital. In both hospitals, most patients could only get supportive therapy.

Mortality rate and risk factors analysis

From 282 admissions in 2015-2017, 136 (48.2%) patients have died. The study population mortality rate was listed in **Table 2**. From 282 patients, within 6 months after being diagnosed with HCC, 56 patients died (23.4%). Within 1 year after being diagnosed with HCC, 90 patients died (45.2%) and 3 years after HCC diagnosis, 134 patients died (94.4%). Bivariate analysis of odds ratio (OR) for each risk factors were listed in **Table 3**. The mortality rates were found higher in CP C score (20% *vs.* 5.5%, p value=0.001), appearance of portal vein thrombus (39.7% *vs.* 26%, p value=0.016), BCLC stage D (21.3% *vs.* 7.5%, p value=0.001), and supportive treatment (54.4% *vs.* 37%, p value=0.006). Multivariate analysis was shown in **Table 4**.

From the multivariate analysis on HCC mortality, based on the

Table 1 The characteristic of HCC patients from each of center in 2015-2017.

Characteristic	Overall HCC Patients (N=282)	HCC Patients from Cipto M Hospital (N=158)	HCC Patients from Dharmais Hospital (N=124)
Sex, n (%)			
Female	71 (25.2%)	45 (28.5%)	26 (21%)
Male	211 (74.8%)	113 (71.5%)	98 (79%)
Age, mean (SD)	55 (12.75)	56 (12.78)	55 (12.75)
Etiology, n (%)			
HBV*	178 (63.1%)	101 (63.9%)	77 (62.1%)
HCV**	48 (17%)	33 (20.9%)	15 (15.1%)
HBV and HCV	10 (3.5%)	10 (6.3%)	0 (0%)
NBNC***	46 (16.3%)	14 (8.9%)	32 (25.8%)
Albumin, mean (SD)	3.50 (0.83)	3.53 (0.66)	3.45 (1.07)
Bilirubin, median (range)	1.20 (0.23-34.58)	1.09 (0.23-22.90)	1.41 (0.29-34.58)
SGOT, median (range)#	87 (1-1613)	78 (11-983)	57 (9-566)
SGPT, median (range)##	46 (3-1331)	42 (3-1331)	114 (1-1613)
Child-Pugh classification, n (%)			
A	137 (48.6%)	84 (53.2%)	53 (42.7%)
B	107 (37.9%)	47 (29.7%)	60 (48.4%)
C	38 (13.5%)	27 (17.1%)	11 (8.9%)
Presence of cirrhosis, n (%)			
No	118 (41.8%)	61 (38.6%)	57 (46%)
Yes	164 (58.2%)	97 (61.4%)	67 (54%)
Vein portal thrombus, n (%)			
No	190 (67.4%)	112 (70.9%)	78 (62.9%)
Yes	92 (32.6%)	46 (29.1%)	46 (37.1%)
HCC Detected during surveillance, n (%)			
No	265 (94%)	141 (89.2%)	124 (100%)
Yes	17 (6%)	17 (10.8%)	0 (0%)
BCLC stadium, n (%)			
A	24 (8.5%)	17 (10.8%)	7 (5.6%)
B	101 (35.8%)	66 (41.8%)	35 (28.2%)
C	117 (41.5%)	56 (35.4%)	61 (49.2%)
D	40 (14.2%)	19 (12%)	21 (16.9%)
Modality therapy, n (%)			
Curative	44 (15.6%)	36 (22.8%)	8 (6.5%)
Palliative	110 (39%)	62 (39.2%)	48 (38.7%)
Supportive	129 (45.4%)	60 (38%)	68 (54.8%)

Notes: *HBV: Hepatitis B Virus; **HCV: Hepatitis C Virus; ***NBNC: Non B Non C; #SGOT: Serum Glutamic Oxaloacetic Transaminase; ##SGPT: Serum Glutamic Piruvic Transaminase; ###BCLC: Barcelona Clinic Liver Cancer

Table 2 The mortality rate of HCC patients.

Variables	Time follow up after diagnosis				
	All time	6 months	1 year	2 years	3 years
Number participate (n)	282	239	199	156	142
Mortality (n)	136	56	90	128	134
Mortality rate (%)	48.2%	23.4%	45.2%	82.1%	94.4%

CP score, the odds ratio increased progressively in CP C patients (OR 1.95; 95% CI 1.08-3.53; p=0.026). The progressive increase was also found in higher Barcelona Clinic Liver Cancer (BCLC) stage of HCC with odds ratio for C and D patients were 3.50 (95% CI 1.18-10.38; p=0.024) and 3.41 (95% CI 1.02-11.41; p=0.047) respectively. The supportive treatment with odds ratio 2.17 (95% CI 1.14-4.16; p=0.019) was found be associated with HCC mortality rate.

Survival rate

From our study, the overall median survival rate was 17 months from the date of diagnosis. If compared between each CP score, CP A had a median survival of 21 months, CP B 17 months, and CP C 9 months (**Figure 1**). From our data, it can be seen that the higher the CP score was, the lower the survival rate became. We also found that the survival rate of each BCLC stage directly

Table 3 Parameters that contribute to all-time mortality.

Parameters	Survivors	Non-survivors	p value
Sex, n (%)			
Female	35 (24%)	36 (26.5%)	0.730
Male	111 (76%)	100 (73.5%)	
Age, n (%)			
<60 years	87 (59.6%)	84 (61.8%)	0.801
≥ 60 years	59 (40.4%)	52 (38.2%)	
Etiology, n (%)			
HBV*	93 (63.7%)	85 (62.5%)	0.939
HCV**	24 (16.4%	24 (17.6%)	
HBV and HCV	6 (4.1%)	4 (2.9%)	
NBNC***	23 (15.8%)	23 (16.9%)	
Child-Pugh classification, n (%)			
A	84 (57.5%)	53 (40%)	0.001
B	54 (37%)	53 (40%)	
C	8 (5.5%)	30 (20%)	
Presence of cirrhosis, n (%)			
No	61 (41.8%)	57 (41.9%)	1.000
Yes	85 (58.2%)	79 (58.1%)	
HCC Detected during surveillance, n (%)			
No	135 (92.5%)	130 (95.6%)	0.323
Yes	11(7.5%)	6 (4.4%)	
Portal vein thrombus, n (%)			
No	108 (74%)	82 (60.3%)	0.016
Yes	38 (26%)	54 (39.7%)	
BCLC stadium, n (%) #			
A	20 (13.7%)	4 (2.9%)	0.001
B	63 (43.2%)	38 (27.9%)	
C	52 (35.6%)	65 (47.8%)	
D	11 (7.5%)	29 (21.3%)	
Modality therapy, n (%)			
Curative	30 (20.5%)	15 (10.3%)	0.006
Palliative	62 (42.5%	48 (35.3%)	
Supportive	54 (37%)	73 (54.4%)	

Notes: *HBV: Hepatitis B Virus; **HCV: Hepatitis C Virus; ***NBNC: Non-B Non-C; #BCLC: Barcelona Clinic Liver Cancer

Table 4 Multivariate analysis.

Analysis	Bivariate	p value	Multivariate	p value
Child-Pugh, n (%)				
A	1	--	1	--
B	1.57 (0.93-2.60)	0.530	1.18 (0.68-2.04)	0.549
C	5.94 (2.53-13.94)	0.025	3.21 (1.16-8.91)	0.025
Portal vein thrombus, n (%)				
No	1	--	--	--
Yes	1.87 (1.13-3.10)	0.016	--	--
BCLC stage, n (%)				
A	1	--	1	--
B	3.02 (0.96-9.49)	0.059	2.90(0.92-9.16)	0.070
C	6.25 (2.01-19.42)	0.002	5.29 (1.67-16.8)	0.005
D	13.18 (3.67-47.33)	0.001	6.71 (1.64-27.48)	0.008
Treatment Modality, n (%)				
Curative	1	--	--	--
Palliative	1.66 (0.79-3.47)	0.179	--	--
Supportive	2.94 (1.42-6.06)	0.004	--	--

decreased proportionally to the increase of BCLC stage. The median survival rates for BCLC B, BCLC C, and BCLC D were 21 months, 14 months, and 9 months respectively (**Figure 2**). Based on the treatment modality, the median survival rate of patients with palliative therapy was 19 months and supportive therapy was 12 months (**Figure 3**).

Discussion

Based on data from WHO 2018, the age-standardized mortality rate of HCC in Indonesia is 7.5 per 100,000 population [1]. The 3-year HCC mortality rate from our multicenter was 94.4%. It can be concluded that three years after being diagnosed with HCC, the majority of patients die.

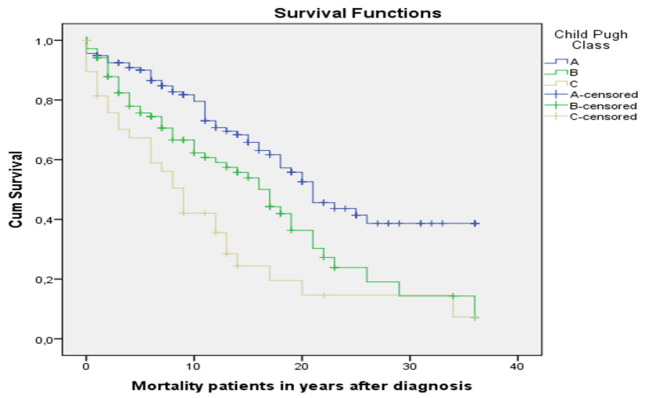

Figure 1 Survival of HCC patients based on Child-Pugh score.

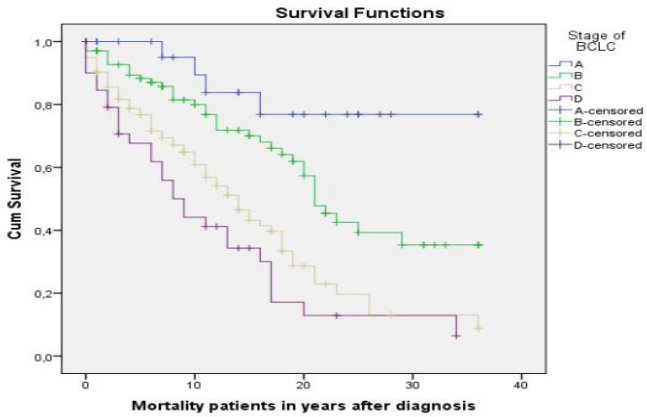

Figure 2 Survival of HCC patients based on BCLC score.

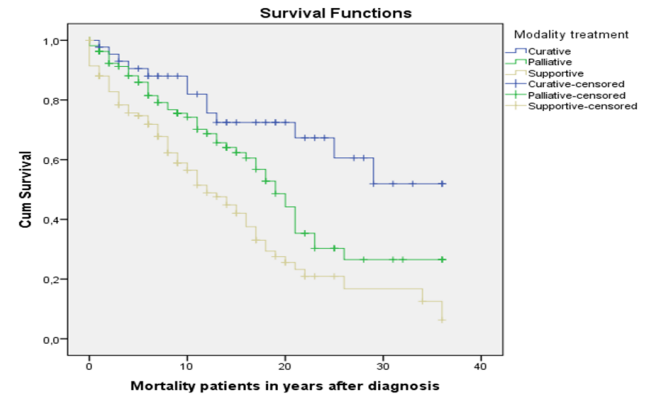

Figure 3 Survival of HCC patients based on therapy.

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide. The incidence is much higher in men and stands as third most common cancer among men and seventh in women [1]. There were 282 patients included this study during the 2015-2017 period. Similar to the study by Loho et al., male is still predominant for HCC which is in accordance to the HCC incidence [2]. In Southeast Asia, the incidence rate of male is >20 per 100,000 population.6 It might be caused by androgen receptor (AR) in male that has been associated with the progressiveness of HCC. It inhibits the P-53 role, DNA repair, and production of oxidative stress. Besides, consumption of alcohol and smoking, which are mostly done by men, have been one of the reasons why more men have HCC than women [6,7].

In our study, the median age of HCC patient was 55-years-old. It is similar to the study by Loho et al., which reported the median age of HCC patients was about 54-years-old. In Asia, especially in high prevalence countries for hepatitis B like Indonesia, HCC diagnosis is under 60-years-old [8].

Interestingly, from our bivariate analysis, age was not associated with HCC mortality. Meanwhile a study by Golabi, et al., explained that age has a risk and reported two years mortality after HCC diagnosis [HR 1.01 (95% CI; 1.01-1.01)] [9]. Fujiwara et al., also studied the significant association between age and mortality [10]. It might be explained that age is only correlated with liver-unrelated death, not related to death. So, it was different with our study because we analyzed the overall HCC mortality whether it was related with liver disease or not. It was also explained that many age-related factors also contributed to mortality, such as the fact that younger patients have good tolerance and overall prognosis [11].

The median age in our study was 55-years-old and was associated with etiology as hepatitis B infection was suffered by younger people [12]. We found the most common cause of HCC was hepatitis B virus (HBV) followed by hepatitis C virus (HCV), non-B non-C, and HBV with HCV. It was reflected in the incidence of HBV infection in Asia as great as 75%, including Indonesia with high prevalence of HBV [6,13]. Some meta-analysis study has found that HBV has a relative risk as much as 15-20 times to become HCC. A study by Loho, et al., in one of our multicenter, reported 14% of patients acquired HCV infection. In our study, HCV infection had increased to 20.9% [2]. It may be caused by the increase of HCV genotype 6 that progressed significantly to HCC in Southeast Asia and also due to the increase in injection drug users [14]. HBV infection was also slightly decreased than the 2013-2014 period, probably caused by HBV vaccination. From our multivariate analysis, the etiology was not associated with HCC mortality. This finding was different from a study by Wei et al., which stated that HBV was related to mortality. In that study, HBV was associated with the age of HCC patients [12]. It claimed that the younger the HBV patients with HCC is, the more rapid it progresses to death. It was different with our study because we did not analyze the association between the HCC patient's age at diagnosis and the mortality rate. We only analyzed the overall age of HCC patients and mortality rate.

To determine the HCC stage, the Barcelona Clinic Liver Cancer (BCLC) has been widely used in clinical practice [5]. Based on our multivariate analysis, stage BCLC C and D were significantly related with mortality (P value BCLC C: 0.024; p value BCLC D: 0.047). The score to determine the liver function or CP score, notably CP C, was also related to mortality. From the data above, we concluded that the higher the BCLC stage and CP C score were, the more significantly they are related to mortality. BCLC stage and CP score had been related to mortality in many studies by Kikuchi et al., reported that HCC with BCLC D had a survival

rate lower than others (HR=4.0, 95% CI: 1.67-9.8; p<0.001) [15]. Likewise, by Khalaf et al., also proved that BCLC stage is related to mortality (p value<0.0001) [16].

The AASLD guideline stated that surveillance is essential and cost-effective for HCC. Surveillance is expected to detect HCC in early stages so curative treatment can commence. In our study, HCC surveillance only found 17 patients (6%). From those 17 patients, 6 were detected with HCC stage BCLC A and 11 were detected with HCC stage BCLC B. The 17 patients (6%) result is similar to the study conducted in the United States stating less than 20% results from HCC surveillance [17]. This small percentage of HCC surveillance in our study were generated solely by Cipto Mangunkusumo General National Hospital. Dhamais Hospital as cancer referral hospital did not have a surveillance program. Therefore, all patients referred to Dharmais Hospital had already been diagnosed with HCC. Most patients (52.9%) with curative treatment were from the HCC surveillance group. Compared to a study in Cipto Mangunkusumo National General Hospital during 2013-2014, the surveillance rate in period 2015-2017 has increased considerably [2]. In 2015-2017, there were 24 people participated in the routine surveillance and 17 patients were diagnosed with HCC while during the 2013-2014 period, there were only 5 people participated in the routine surveillance and 2 patients were diagnosed with HCC. This increase was due to the possibility of more frequent visits to hepatologists and the patients were already diagnosed as decompensated cirrhosis with ascites and encephalopathy. In contrast, patients with fewer symptoms will not come to hepatologists for surveillance. Besides that, the lack of physician's awareness and risk factors screening program in our population might also contribute to the low level of HCC surveillance. This leads to an increasing number of HCC mortality despite its considerable preventive measures, screening tools, and treatment modalities [18,19].

Interestingly, in our multivariate analysis, surveillance did not correlate with mortality. It was different from a meta-analysis study conducted by Singal et al., [20] which reported that HCC surveillance could improve survival rate (pooled odds ratio: 1.90; 95% CI; 1.67-2.17). However, some other studies also found that HCC surveillance did not correlate with mortality and stating that the treatment should start since the initial HCC diagnosis [21]. The reason why surveillance did not correlate with mortality in our study was that our surveillance data came from only one multicenter resulting a bias and unproportional data.

In our study, the treatment was dominated by supportive treatment followed by palliative and curative. It was because many patients had been diagnosed with advanced stage HCC when referred to our multicenter. In our multivariate analysis, the risk of mortality also related to treatment. Supportive treatment had a significant association with mortality because patients who received supportive care were patients with high BCLC and CP score, both of which were also associated with HCC mortality. From this data, we can conclude that curative therapy was very important in reducing HCC mortality. A study conducted by Golabi et al., stated that HCC therapy with liver transplant as curative treatment can reduce mortality in 2 years' time [9].

There are 3 factors associated with HCC mortality. The survival rate between each factors showed that an increase in each CAP score stage BCLC stage was followed by a decrease in the survival rate. This can be seen from the Kaplan Meier chart. In addition, patients underwent supportive treatment had lower survival rates than other treatment modalities.

In our study, the HCC mortality rate in 3 years from our multicenter was 94.4%. It can be concluded that three years after being diagnosed with HCC, the majority of patients die.

The strength of our study lies in the discussion on the relationship between risk factors and HCC mortality which has never been discussed before, particularly in Indonesia. However, our study has a limitation concerning the lack of follow up data because many patients were unable to be reached. Therefore, we cannot examine several variables regarding HCC mortality, such as AFP or tumor size.

Conclusion

In conclusion, the risk factors related significantly with HCC mortality were BCLC stage, CP score, and treatment modality. The greater BCLC stage or Child-Pugh score is, the greater it is related to HCC mortality. Supportive treatment was associated with high HCC mortality. We suggest increasing HCC surveillance to detect earlier stages of HCC which can undergo curative treatment, has better prognosis and also lower mortality rate. For future studies, we recommend that other parameters can also be examined.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 1: 1-31.

2 Loho IM, Hasan I, Lesmana CRA, Dewiasthi A, Gani RA (2016) Hepatocellular carcinoma in a tertiary referral hospital in Indonesia: Lack of improvement of one-year survival rates between 1998-1999 and 2013-2014. Asian Pac J of Cancer Prev 17: 2165-2170.

3 Janevska D, Chaloska-Ivanova V, Janevski V (2015) Hepatocellular carcinoma: Risk factors, diagnosis and treatment. Open Access Maced J Med Sci 3: 732-736.

4 Yano Y, Utsumi T, Lusida MI, Hayashi Y (2015) Hepatitis B virus infection in Indonesia. World J Gastroenterol 21: 10714-10720.

5 Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: An update. Hepatology 53: 1020-1022.

6 Ashtari S, Pourhoseingholi MA, Sharifian A, Zali MR (2015) Hepatocellular carcinoma in Asia: Prevention strategy and planning. World J Hepatol 7: 1708-1717.

7 Ma W, Lai H, Yeh S, Cai X, Chang C (2014) Androgen receptor roles in hepatocellular carcinoma, cirrhosis, and hepatitis. Endocr Relat Cancer 21: 165-182.

8 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS (2018) Diagnosis, staging, and management of hepatocellular carcinoma: 2018

practice guidance by the American Association for the study of Liver diseases. Hepatology 68: 723-750.

9 Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, et al. (2017) Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine 5: 2824-8853.

10 Fujiwara N, Tateishi R, Kondo M, Minami T, Mikami S, et al. (2014) Cause-specific mortality associated with aging in patients with hepatocellular carcinoma undergoing percutaneous radiofrequency ablation. European Journal of Gastroenterology &Hepatology 26: 1039-1046.

11 Xu X, Chen W, Miao R, Zhou Y, Whang Z, et al. (2015) Survival analysis of hepatocellular carcinoma: A comparison between young patients and aged patients. Chinese Medical Journal 128: 1793-1800.

12 Wei XL, Luo HY, Li CF, Jin Y, Zeng ZL, et al. (2017) Hepatitis B virus infection is associated with younger median age at diagnosis and death in cancers. Int J Cancer 141: 152-159.

13 Sulaiman HA, Julitasari, Sie A, Masri R, Melani W, et al. (1995) Prevalence of hepatitis B and C viruses in healthy Indonesia blood donors. Trans R Soc Trop Med Hyg 89: 167-70.

14 Lee MH, Hsiao TI, Subramaniam SR, Le AK, Vu VD, et al. (2017) HCV genotype 6 increased the risk for hepatocellular carcinoma among Asian patients with Liver cirrhosis. Am J Gastroenterol 112: 1111-1119.

15 Kikuchi L, Chagas AL, Alencar RSSM, Tani C, Diniz MA, et al. (2017) Adherence to BCLC recommendations for the treatment of hepatocellular carcinoma: Impact on survival according to stage. Clinics 72: 454-460.

16 Khalaf N, Ying J, Mittal S, Temple S, Kanwal F, et al. (2017) Natural history of untreated hepatocellular carcinoma in a US cohort and the role of cancer surveillance. Clinical Gastroenterology and Hepatology 15: 273-281.

17 Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA (2010) Utilization of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology 52: 132-41.

18 Mohammed HAA, Yang JD, Giama NH, Choi J, Ali HM, et al. (2017) Factors influencing surveillance for hepatocellular carcinoma in patients with liver cirrhosis. Liver Cancer 6: 126-136.

19 Putra AP, Sulaiman AS, Kurniawan J, Harimurti K (2017) Factors associated with surveillance for early detection of hepatocellular carcinoma in liver cirrhosis patients. The Indonesian Journal of Gastroenterology, Hepatology and Digestive Endoscopy 18: 153-158.

20 Singal AG, Pillai A, Tiro J (2014) Early detection, curative treatment and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: A meta-analysis. PLoS Med 2: 2469-11105.

21 Moon AM, Weiss NS, Beste LA, Su F (2018) No association between screening for hepatocellular carcinoma and reduced cancer-related mortality in patients with cirrhosis. Gastroenterology 155: 1128-1139.