Incidence and Factors of Hepatocellular Carcinoma in Hepatitis C Virus Patients Achieving Sustained Virological Response After Direct-Acting Antiviral Treatment

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ABSTRACT

***Background**: The incidence and risk factors for Hepatocellular Carcinoma (HCC) in Hepatitis C Virus (HCV) patients who have achieved Sustained Virological Response (SVR) after Direct-Acting Antiviral (DAA) therapy are not well established. Considering there are differences in DAA types, virus genotypes, and patient profiles in Indonesia, this study was conducted to assess the incidence and factors influencing HCC in HCV patients after SVR post DAA therapy. The objective of this study to determine the incidence and factors influencing HCC in HCV patients achieving SVR after DAA treatment.*

***Methods**: Retrospective cohort study conducted at Cipto Mangunkusumo National General Hospital, sample of HCV patients had SVR after DAA therapy in 2017 – 2019, followed until 2024. Patients were screened for abdominal ultrasound, alpha-fetoprotein (AFP) and 3-phase abdominal CT scan, if indicated. Descriptive, bivariate analysis with Fisher's exact, and multivariate analysis with logistic regression were conducted.*

***Results**: Among 180 subjects, the incidence and incidence ratio of HCC is 4.4% (0.91/100PY). Significant correlation in bivariate analysis from the variables liver cirrhosis (RR 10.5; CI 95% (1. 32 – 83.5); p = 0.0073) and type 2 DM (RR 8.47; CI 95% (2, 3 – 31.1) p = 0.0048). In multivariate analysis, there was significant correlation from type 2 DM variable (aRR 3.1; CI 95% (0.86 – 3.83); p=0.002).*

***Conclusion**: The incidence of HCC reaches 4.4% of the total population. Type 2 DM has significant correlation with the incidence of HCC in HCV patients who achieve SVR after DAA treatment.*

***Keywords**: Direct-Acting Antiviral, Hepatitis C Virus, Hepatocellular Carcinoma, Incidence, Sustained Virological Response*

ABSTRAK

***Latar belakang**: Insidensi dan faktor risiko Karsinoma Hepatoseluler (KSH) pada pasien Hepatitis C Virus (HCV) yang sudah mencapai Sustained Virological Response (SVR) pasca terapi Direct Acting Antiviral (DAA) belum banyak diketahui. Mengingat terdapat perbedaan jenis DAA, genotype virus, dan profil pasien di Indonesia, dilakukan studi untuk menilai insidensi dan faktor-faktor yang memengaruhi KSH pada pasien HCV pasca SVR post terapi DAA. Tujuan penelitian ini adalah untuk mengetahui insidensi dan faktor-faktor yang memengaruhi kejadian KSH pada pasien HCV yang mencapai SVR pasca pengobatan DAA.*

***Metode:** Desain penelitian kohort retrospektif di lakukan di RSUPN Cipto Mangunkusumo menggunakan sampel pasien HCV yang SVR pasca DAA tahun 2017 – 2019, diikuti hingga 2024. Pasien dilakukan skrining USG abdomen, Alpha-Fetoprotein (AFP) dan CT Scan abdomen 3 fase apabila terdapat indikasi. Dilakukan analisis deskriptif, bivariat dengan Fisher's exact, dan multivariat dengan regresi logistik bila terdapat faktor risiko di analisis bivariat (p <0,25).*

***Hasil:** Dari 180 subjek penelitian, insidensi, dan rasio insidensi KSH pada seluruh populasi mencapai 4,4% (rasio insidens 0,91/100PY). Terdapat hubungan signifikan dari analisis bivariat variabel sirosis hepatis (RR 10,5; IK 95% (1,32 – 83,5); p =0,0073) dan DM tipe 2 (RR 8,47; IK 95% (2,3 – 31,1) p = 0,0048). Terdapat hubungan signifikan dari analisis multivariat variabel DM tipe 2 (aRR 3,1; IK 95% (0,86 – 3,83); p=0,002).*

***Simpulan:** Insidensi KSH mencapai 4,4% dari total populasi. DM tipe 2 memiliki hubungan yang signifikan terhadap kejadian KSH pada pasien HCV yang mencapai SVR pasca pengobatan DAA.*

***Kata kunci:** Antivirus kerja langsung, Virus Hepatitis C, Karsinoma Hepatoseluler, Insiden, Respons Virologi Berkelanjutan*

INTRODUCTION

The global burden of disease caused by hepatitis viruses is increasing. In 2013, viral hepatitis was ranked seventh as the most common cause of death worldwide.[1] Hepatitis C virus (HCV) infection is one of the most common and deadly hepatitis infections worldwide, with a worldwide prevalence reaching 170 million people[2-4], this is caused by complications of hepatitis C virus, namely liver cirrhosis to Hepatocellular Carcinoma (HCC).[5, 6]

Continued discoveries in molecular biology gave rise to a new generation of drugs, currently called direct acting anti-virals (DAAs). The DAA regimen, as its name suggests, inhibits the action of enzymes and cofactors in the HCV structure or its products. The results of the DAA regimen treatment have a high sustained viral response (SVR), reaching 90% after 12 weeks of treatment.[7] However, hepatitis C patients who have been treated using DAA and achieved SVR, can still develop HCC. This is believed to be due to a sudden decrease in viral load causing distortion of the immune system, and deregulation of the anti-tumor response resulting in the release of pre-cancerous foci from immune system surveillance.[7]

Although SVR is associated with a reduction in several pathogenetic factors of HCC, many other factors contribute to the occurrence of HCC, such as the stage of liver disease (e.g., Child-Pugh score B, portal hypertension, low platelets)[8,9] or the presence of comorbidities, such as diabetes, HIV co-infection, hepatitis B co-infection, non-alcoholic fatty liver disease (NAFLD), alcohol consumption, smoking, and old age.[10-12]

Considering the differences in direct-acting antiviral regimens in Indonesia, differences in hepatitis C genotypes in Indonesia, differences patient profiles, differences in patient habits, unclear risk factors for HCC in HCV patients in Indonesia, accompanied by research that has never been conducted on the outcomes of hepatitis C patients who have achieved SVR after DAA therapy in Indonesia, the researchers examined the incidence and factors. factors influencing hepatocellular carcinoma in hepatitis C virus patients who have achieved SVR post DAA therapy.

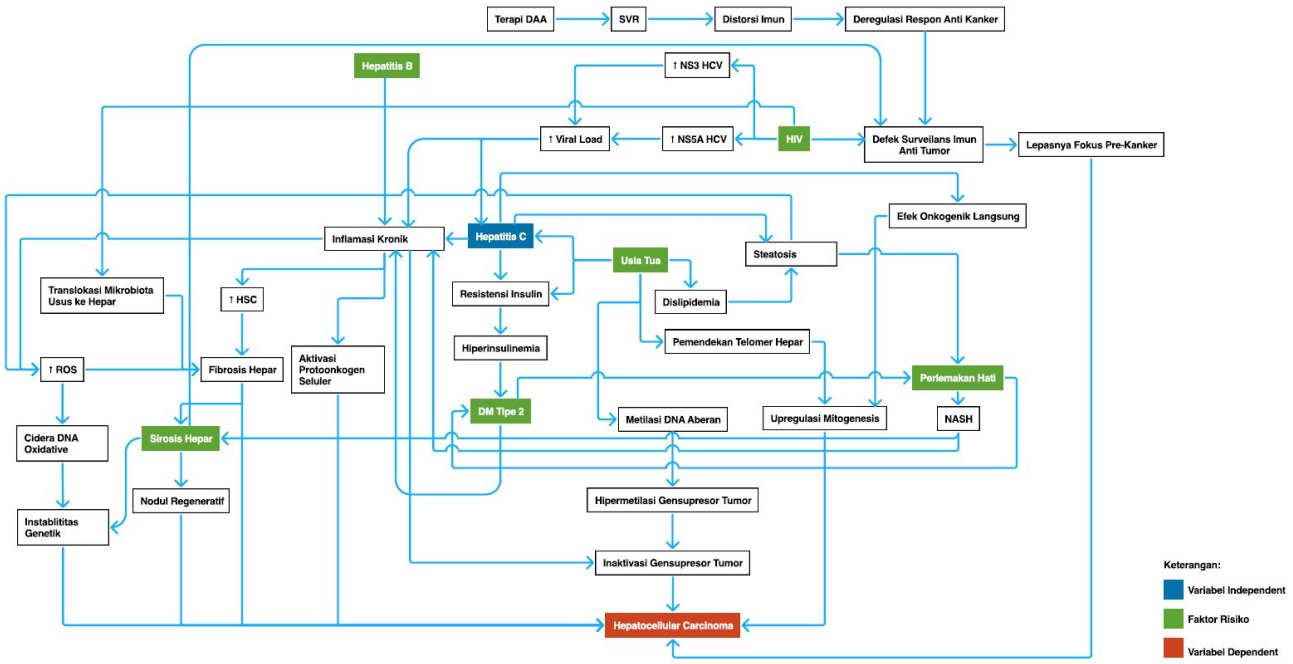

Figure 1. Theoretical Framework

METHODS

Population and Study Design

This research is a retrospective cohort study with primary data collection on hepatitis patients. The accessible population is adult patients with hepatitis C virus infection who have achieved SVR after being treated with DAA in 2017 – 2019. The inclusion criteria in this study were patients with chronic hepatitis C virus, using DAA therapy, who had achieved SVR and were aged ≥18 years. The exclusion criteria in this study were incomplete medical record data and patients with a history of HCC/diagnosed, with HCC before therapy or having HCC within 6 months after therapy. The protocol of the research had been ethically accepted by the Research Ethics Committee of the Faculty of Medicine, University of Indonesia (No.60/UN2.F1/ETIK/PPM.00.02/2024).

Data Collection and Sampling Method

Data collected included basic data and patient characteristics (age, gender, year of SVR, history of liver cirrhosis, diabetes mellitus, HIV co-infection, hepatitis B co-infection, and NAFLD. The research was conducted at the Department of Internal Medicine, Faculty of Medicine, University of Indonesia, National Central General Hospital Dr. Cipto Mangunkusumo (RSCM) from 2023 – 2024. Sampling will be carried out by total sampling, namely every post-SVR chronic hepatitis C patient with DAA treatment will be involved in this research until sample requirements are met.

The research samples were checked periodically every 6 months, over a period of 3 years or more using an abdominal ultrasound examination carried out in the RSCM Hepatobiliary Integrated Procedure Room and an Alpha-Fetoprotein (AFP) lab examination, if there were nodules measuring 1-2 cm or > 2 cm and/or an increase in AFP, a 3-phase abdominal CT scan will be carried out to confirm the diagnosis of Hepatocellular Carcinoma. Monitoring research samples for more than 3 years, data collection is still carried out. Abdominal ultrasound examination will be carried out in the RSCM Hepatobiliary Integrated Procedure Room. Abdominal CT Scan examinations are carried out in the Radiology room at FKUI RSCM. All inspection techniques are carried out in accordance with applicable operational standards.

Statistical Analysis of The Data

Primary data was processed using the Stata 15.1 computer program. The statistical analysis used was: univariate analysis, and bivariate analysis was carried out between each risk factor and HCC. From bivariate analysis with the Fisher's Exact test (because it does not meet the chi-square requirements), a crude relative risk (RR) will be obtained along with a 95% confidence interval (CI) for each of these factors. To avoid bias from each factor, a multivariate analysis was carried out using the logistic regression method on the risk factor variables, which in bivariate analysis gave a p value of <0.25.

RESULTS

Characteristics of Study Population

We identified 252 patients who had SVR undergoing DAA therapy. We excluded a total of 72 patients, with details, 8 patients with HCC before SVR, 2 patients with HCC <6 months before SVR, 17 patients with incomplete data and 45 patients refused the study. A total of 180 patients were included in the final analysis. In this study, the majority of research subjects were male with a total of 119 patients (66.11%), 61 patients (33.89%) female. In the age group, the majority of research subjects had a median age of 47 (23 - 91) years. Based on the tumor marker value profile, the median AFP was 2.88 (0.96 – 22,722). The characteristics of the subjects in the study based on risk factors were as follows: 34 patients (18.8%) without risk factors, the majority of research subjects were aged ≥ 55 years 54 patients (30%), cirrhosis of liver 72 patients (40%), patients with HIV 63 patients (35%), co-hepatitis B 6 patients (3.33%), DM type 2 19 patients (10.56%), NAFLD 42 patients (23.33%).

If the characteristics were stratified based on HCC (8 patients), non-HCC (172 patients), in the HCC population, liver cirrhosis was found in 7 patients, with a male predominance in 7 patients (85.7%). Patients with HCC had a higher median age of 57 (45 – 91) years, compared to non-HCC 47 (23 – 83) years. Patients with HCC also had a higher median AFP value of 125.23 (3.58 – 22,722) ng/mL compared to non-HCC 2.79 (0.95 – 22.97) ng/mL. In the HCC population with cirrhosis, if stratification was carried out based on risk factors, there were 4 patients (57.14%) with type 2 DM, 3 patients aged ≥55 years (42.86%), then the risk factors were HIV, hepatitis B and NAFLD. each obtained 1 patient (12.5%).

Table 1. Baseline Characteristics of Study Population

Characteristics	Study Population
Sum of Study Population, n (%)	180 (100%)
Gender	
Male, n (%)	119 (66,11%)
Female	61 (33,89%)
Age, Median (Q1 – Q3)	47 (43 – 56,5)
BMI, Mean (±SD)	24 ± 4,7
Risk Factors Profile	
Age	
≥55, n (%)	54 (30%)
<55	126 (70%)
Hepatic Cirrhosis	
Yes, n (%)	72 (40%)
No	108 (60%)
HIV Co-infection	
Yes, n (%)	63 (35%)
No	117 (65%)
Hepatitis B Co-infection	
Yes, n (%)	6 (3,33%)
No	174 (96.67%)
Fatty Liver	
Yes, n (%)	42 (23,33%)
No	138 (76,67%)
Type 2 Diabetes	
Yes, n (%)	19 (10,5%)
No	161 (89,5%)
Observation periods, Years (Min-Max)	5 (1 – 6)

Table 2. Baseline characteristics of research subjects based on HCC and non-HCC

Variable	HCC (n =8)		Non-HCC (n =172)	
	Cirrhosis (n=7)	Non-Cirrhosis (n=1)	Cirrhosis (n=65)	Non-Cirrhosis (n=107)
Gender				
Male	6 (85,7%)	1 (100%)	38 (58,5%)	74 (69,1%)
Female	1 (14,3%)	0 (0%)	27 (41,5%)	33 (30,9%)
Ages (years)				
Median (Q1-Q3)	57 (50 – 70,5)		47 (42 – 56)	
Risk Factors Profile				
Age				
≥55, n(%)	3 (42,86%)	1 (100%)	31 (47,7%)	18 (16,8%)
<55	4 (57,14%)	0 (0%)	34 (52,3%)	89 (83,2%)
HIV Co-infection				
Yes, n(%)	1 (14,3%)	0 (0%)	12 (18,5%)	50 (46,7%)
No	6 (85,7%)	1 (100%)	53 (81,5%)	57 (53,3%)
Hepatitis B Co-infection				
Yes, n(%)	1 (14,3%)	0 (0%)	1 (1.5%)	4 (3,7%)
No	6 (85,7%)	1 (100%)	64 (98.5%)	103 (96,3%)
Type 2 Diabetes				
Yes, n(%)	4 (57,14%)	0 (0%)	11 (16,9%)	4 (3,7%)
No	3 (42,86%)	1 (100%)	54 (83,1%)	103 (96,3%)
Fatty Liver				
Yes, n(%)	1 (14,3%)	0 (0%)	6 (9,2%)	35 (32,7%)
No	6 (85,7%)	1 (100%)	59 (90,8%)	72 (67,3%)

HCC Incidence

The incidence of HCC was found to be 8 patients (4.44%) from the total population. If stratification was carried out based on cirrhosis and non-cirrhosis, the HCC proportion was found to be 7 patients (9.7%) in the cirrhosis population and 1 patient (0.9%) in the non-cirrhosis population. With an incidence ratio of 0.91 per 100 person-years (PY) for the entire population, 2.1 per 100 PY for the cirrhotic population and 0.18 per 100 PY for the population without cirrhosis. The median observation was 5 (1 – 6) years since SVR after initiation of DAA therapy. In the HCC population, the average incidence of HCC was obtained after observation at 33.6 ± 10.45 months after SVR. The cumulative incidence in years -1, -2, -3, and -4, in the cirrhotic and non-cirrhotic population can be seen in the Nelson-Aalen curve below.

Analysis between risk factors and the incidence of HCC

There is a significant relationship between liver cirrhosis (p = 0.0073) and the relative risk (RR) (10.5 (1.32 – 83.5) with the incidence of HCC. The type 2 DM variable also has a significant relationship (p = 0.0048) with relative risk (RR) (8.47; 95% CI 2.3 – 31.1) for the incidence of HCC. Age ≥ 55 years did not have a significant relationship with HCC with (p = 0.0538) with relative risk (RR) (3.88; 95% CI 0.96 – 15.6) on the incidence of HCC. In the bivariate analysis between HIV co-infection, hepatitis B co-infection, and NAFLD, no significant relationship was found with the incidence of HCC. -respective variables, HIV co-infection (p = 0.2641), hepatitis B co-infection (p = 0.2417), and NAFLD (p = 0.6831).

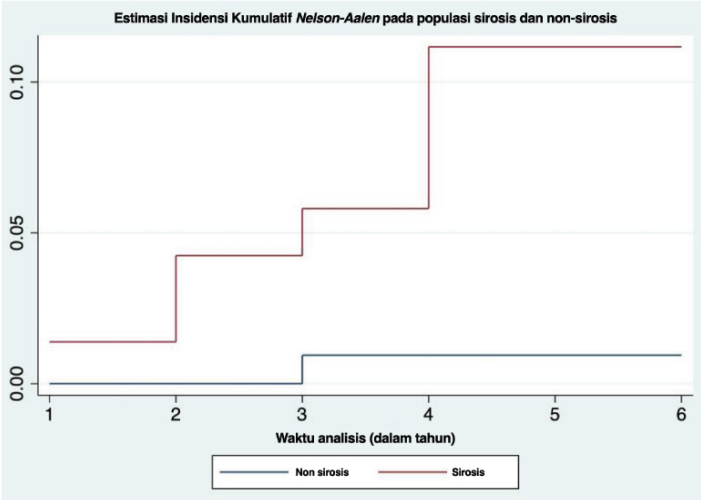

Figure 2. Nelson-Aalen cumulative incidence estimates in cirrhotic and non-cirrhotic populations

Table 3. Bivariate analysis between risk factors and the incidence of HCC

Variable	HCC		Total	P value	RR (CI 95%)
	Yes n (%)	No n (%)			
Age ≥ 55 years					
≥ 55	5 (9,2%)	49 (90,8%)	54	0,0538[f]	3,88 (0,96 – 15,6)
< 55	3 (2,4%)	123 (97,6%)	126		
Hepatic Cirrhosis					
Ya	7 (9,7%)	65 (90,3%)	72	0,0073[f]	10,5 (1,32 – 83,5)
Tidak	1 (0,9%)	107 (99,1%)	108		
Type 2 DM					
Yes	4 (21%)	15 (79%)	19	0,0048[f]	8,47 (2,3 – 31,1)
No	4 (2,5%)	157 (97,5%)	161		
HIV Co-infection					
Yes	1 (1,6%)	62 (98,4%)	63	0,2641[f]	0.24 (0.03 – 2,1)
No	7 (5,9%)	110 (94,1%)	117		
Hepatitis B Co-infection					
Yes	1 (16.7%)	5 (83.3%)	6	0,2417[f]	4,14 (0,6 – 28,5)
No	7 (4%)	167 (96%)	174		
Fatty liver					
Yes	1 (2,4%)	41 (97,6%)	42	0,6831[f]	0,47 (0,06 – 3,7)
No	7 (5%)	131 (95%)	138		

[f] Fisher's exact test

Table 4. Multivariate analysis between risk factors and the incidence of HCC

Variable	HCC		Total	P value	aRR (CI 95%)
	Yes n (%)	No n (%)			
Age ≥ 55 years					
≥ 55	5 (9,2%)	49 (90,8%)	54	0.372	0,89 (-0,97 – 2,59)
< 55	3 (2,4%)	123 (97,6%)	126		
Hepatic Cirrhosis					
Ya	7 (9,7%)	65 (90,3%)	72	0.145	1,46 (-0,58 – 3,96)
Tidak	1 (0,9%)	107 (99,1%)	108		
Type 2 DM					
Yes	4 (21%)	15 (79%)	19	0.002	3,1 (0,86 – 3,83)
No	4 (2,5%)	157 (97,5%)	161		
Hepatitis B Co-infection					
Yes	1 (16.7%)	5 (83.3%)	6	0,158	1,41 (-0,76 – 4,69)
No	7 (4%)	167 (96%)	174		

The variables age, hepatitis B, type 2 DM and liver cirrhosis were included in the multivariate analysis. Based on the results of the multivariate analysis, it was found that the type 2 DM variable was the only significant variable with a p value (0.002) and an accumulative risk ratio (aRR) of 3. 1 (0.86 – 3.83).

In this study, additional analysis was also carried out to determine the effect of the stage of child-pugh scoring on the incidence of HCC. It was found that patients with child-pugh scores B≥8 and C had an RR of 15.5 (3.47 – 69.3) with p = 0.0003 for the occurrence of HCC when compared with child-pugh scores A and B (7).

DISCUSSION

In this study, a cohort of 180 patients with hepatitis C who had SVR after DAA therapy was conducted, followed for a median time of 5 (1 – 6) years after SVR. A total of 8 patients (4.4%) were diagnosed with HCC, with a HCC proportion of 7 patients (9.7%) in the cirrhosis population and 1 patient (0.9%) in the non-cirrhosis population. The mean incidence of HCC was found to be 33.6 ± 10.45 months after SVR. Overall, the results of the incidence of HCC obtained in this study are identical to the research of Leal, et al., in Brazil, the median follow-up time for HCC was 40 months, the incidence of HCC was 5.9% in 5 years, with an incidence ratio of 1.46 per 100 PY for the overall population, 2.31 per 100 PY in the cirrhotic population, and 0.2 per 100 PY in the non-cirrhotic population.[13-15]

When compared with other studies in hepatitis C populations without cirrhosis, the HCC incidence ratio results in this study were lower (0.18 per 100 PY) compared to Taiwan (0.65 per 100 PY), with population risk factors in Taiwan having a high value of HCV RNA and alanine transaminase (ALT). In the cirrhotic population, the HCC incidence ratio results of this study were lower (2.1 per 100 PY) compared to Korea (6.4 per 100 PY) and Japan (5 – 8 per 100 PY), while similar to the results in the United States (1 – 4%). These results suggest that oriental populations/ countries with/or without cirrhosis caused by HCV have a higher incidence rate, with the hypothesis that there are differences in diet, smoked foods, genetics and aflatoxin exposure.[5]

In this study, a significant relationship was found between the variables liver cirrhosis and type 2 DM. For the type 2 DM variable, the bivariate RR value (RR 8.47, 95% CI 2.3 – 31.1) (p=0.0048), and aRR multivariate (3.1, 95% CI 0.86 - 3.83) (p = 0.002). These results are supported by several studies, including research by Abe, et al.,[16] which states that DM and cirrhosis are strong risk factors for HCC after SVR is obtained. Similar to Hagiwara, et al, who also stated that the presence of type 2 DM was a factor that was associated (p=0.012) with the incidence of HCC in hepatitis C patients after DAA-SVR with multivariate HR (3.4, 95% CI 1.266 – 9.132). [17] Although many studies support the presence of type 2 DM as a factor related to the incidence of HCC, there are several studies which state that there is no relationship between the incidence of HCC and type 2 DM.[5, 18, 19]

The liver cirrhosis variable has a significant relationship with the incidence of HCC, RR (10.5; 95% CI (1.32 – 83.5)) (p = 0.0073), although after being included in the multivariate analysis it becomes not significant (p = 0.145) with aRR (1.46; 95% CI (-0.58 – 3.96). From additional analysis, it was found that cirrhotic patients with child-pugh scores B≥8 and C had an RR of 15.5 (3.47 – 69.3) with p = 0.0003 for the occurrence of HCC when compared with Child-Pugh scores A and B (7), which means that in patients with advanced stages of cirrhosis, the risk of HCC is increasing. Similar to research in America South, with a 5-year cohort analysis of the incidence of HCC, it was found that the incidence of HCC was higher in cirrhotic

patients than non-cirrhotic patients (9.7% vs 1.6%, p <0.0001)., et al [13, 18,] who assessed the risk factors for HCC in post-SVR hepatitis C patients in America and China, said that the most consistent variable as a predictor of HCC was cirrhosis.

In a study by Kurniawan, et al, said that in cirrhotic patients with type 2 DM, the ability of insulin to suppress hepatic gluconeogenesis is reduced, and the degradation of hepatic insulin is reduced, this causes hyperinsulinemia, which initially helps treat insulin resistance, but over time causes hyperglycemia. Insulin itself will bind to the insulin receptor which will activate several signaling pathways through Insulin-like growth factors (IGF-1), Ras-MAPK, PI3K-Akt, and mTOR which ultimately play a role in inflammation, cell proliferation and inhibition of apoptosis. When chronic liver disease occurs, hepatocytes, which avoid apoptosis and necrosis, are faced with various factors such as inflammation, hyperglycemia, oxidative stress and increased levels of free fatty acids, which leads to hepatocarcinogenesis.[20] So it can be concluded that there is a complex relationship between type 2 DM, insulin and the occurrence of HCC may be caused by a process of prolonged hyperinsulinemia and hyperglycemia, which indicates an advanced stage of type 2 DM.

After therapy with DAA, there is an important mechanism called reversibility of liver fibrosis. A meta-analysis stated that there was a significantly reduced risk of HCC after SVR, especially in patients with cirrhosis (22%; 95% KI 13 – 31), compared to any stage of fibrosis (6.7%; 95% KI 5 – 8). [12] This is supported by the study of Masuzaki, et al., which states that the incidence of HCC over 5 years increases with the height of the liver stiffness measurement (LSM): 9.7% for transient elastography (TE) ≥ 15 kPa, and 11.4% TE ≥ 20 kPa.[21] So, even though it is not directly related to the incidence of HCC, assessment of liver fibrosis can act as a predictor to determine whether a population is still at risk for HCC or not, so that tests can be carried out to assess liver fibrosis after SVR, especially in patients with non-SVR examinations. invasive such as transient elastography, ALBI, APRI, FIB-4 to non-invasive serological markers to assess fibrosis regression after DAA-SVR.

Based on this description, a conclusion can be drawn, that hepatocellular carcinoma can still occur after SVR in hepatitis C patients after DAA therapy, especially in the population of liver cirrhosis patients with risk factors for type 2 DM and old age. It should also be noted in populations with other risk factors as follows: (1) nodules without characteristics before DAA, (2) albumin levels <4g/dL at SVR, (3) AFP >4.1 ng/mL at SVR, (4) platelet count <82,000/μL pre-therapy and (5) family history of HCC, because based on literature[13,16,17], these findings are also related to the incidence of HCC. Considering the increased risk of HCC in the cirrhotic population with risk factors for type 2 DM and old age, it is possible to adapt according to Japanese guidelines, [17] which carry out surveillance every 3 - 4 months, especially in patients with advanced fibrosis (F3) or cirrhosis (F4). accompanied by risk factors for type 2 DM and age ≥ 55 years.

This study has several advantages. First, best of the author's knowledge, this study is the first study in Indonesia, to the, to study the incidence and risk factors for HCC in HCV patients. Second, data collection in this study used a retrospective cohort method taken in real-time at tertiary hospitals in Indonesia, with a sufficient duration of up to 7 years. Third, in this study, the use of standardized protocols, manual procedures and diagnostic criteria means that basic characteristic data can be collected completely and well, so that risk factors and causal relationships can be well defined and increase the confidence index of the results of this study.

This study has several limitations, first, the risk factor variables are limited, while there are other risk factor variables, such as duration of cirrhosis, fibrosis regression, family history of HCC, and blood sugar values, with the presence of these risk factors, it is estimated that the cut-off from the laboratory can be calculated as reference for increasing the risk of HCC. Second, the profile of diabetes mellitus in the risk factor variable only uses DM and no DM. Considering the significance of the DM variable in this study, it would be better if the type 2 DM variable was known whether controlled or not/using insulin or not. Third, in research related to malignancies, the duration of monitoring is limited, so there is a possibility that patients who are currently being screened will experience HCC in the future. Lastly, the sample size is not too large which might influence the research results.

Early detection and early therapy are important to improve prognosis, making it important as clinicians to emphasize surveillance in at-risk populations. Based on the 2022 national guidelines for HCC medical services, HCC surveillance is carried out using liver ultrasound and measuring levels of AFP and/or protein induced by vitamin K absence or antagonist-II (PIVKA-II) in the blood every 6 months, especially in at-risk populations including patients child-pugh liver cirrhosis A and

B, as well as non-cirrhotic chronic hepatitis C with advanced liver fibrosis (F3).[22] Slightly different from Japan, surveillance with ultrasound and AFP and/or PIVKA-II is carried out every 6 months in patients with chronic hepatitis and every 3 – 4 months in patients with cirrhosis.[17] Indonesia may be able to adapt by conducting surveillance every 3 – 4 months, especially in patients with advanced fibrosis (F3) or cirrhosis (F4) accompanied by risk factors for type 2 DM and age ≥ 55 year.

CONCLUSION

The incidence of hepatocellular carcinoma in chronic HCV patients who achieved SVR post DAA treatment reached 4.4% with an incidence ratio of 0.91 PY. Type 2 DM is the risk factor most associated with increasing the incidence of hepatocellular carcinoma in chronic HCV patients who achieve SVR post DAA treatment.

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