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Research Article

THE INCIDENCE OF LIVER FIBROSIS BASED ON NON-INVASIVE MARKERS AND HEPATOTOXIC DRUG USED IN HEPATITIS B PATIENTS

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ABSTRACT

Objective: The development of hepatitis B virus infection can lead to the asymptomatic liver fibrosis, which is reversible, but can develop into cirrhosis or even carcinoma. Hence, laboratory markers are needed to acquire the incidence of fibrosis such as by using aspartate aminotransferase (AST)-to-platelet ratio index (APRI), Fib-4, AST-alanine aminotransferase ratio (AAR), age-platelet (AP) index, and Pohl score. The use of hepatotoxic drug is commonly found in hepatitis B patients that might increase the risk of liver damage. This study aimed to determine the prevalence of liver fibrosis and to discover the use of hepatotoxic drug in hepatitis B patients at Prof. Dr. Margono Soekardjo Purwokerto General Hospital, Indonesia.

Methods: This study used total sampling methods with descriptive qualitative and quantitative analysis. The source of data was medical records of hepatitis B patients from January 2012 to August 2013.

Results: The result showed that from 25 hepatitis B patients, the incidence of liver fibrosis was found in 8% patients based on APRI, 44% based on Fib-4, 60% based on AAR, 52% based on AP index, and 28% based on Pohl score. There were 12 kinds of hepatotoxic drugs with ranitidine (60%) as the drug most widely used, and most of them used one kind of hepatotoxic drug.

Conclusions: Our study found that the incidence of liver fibrosis was found in hepatitis B patients, which was measured based on APRI, Fib-4, AAR, AP index and Pohl score, beside that the use of hepatotoxic drug was commonly found among those patients.

Keywords: Hepatitis B, Liver fibrosis, Non-invasive marker, Hepatotoxic drug.

INTRODUCTION

Hepatitis B virus is the most general cause of chronic liver disease that happen around the world, which in its development can cause liver fibrosis, cirrhosis, and hepatocellular carcinoma [1]. The prevalence of hepatitis B occurrence in Indonesia reached 23 millions of people or 9.4%. Meanwhile, the rate of death which caused by liver cirrhosis and carcinoma in Asia and Africa is estimated from 500.000 to 1.2 million per year, in addition the prevalence in South East Asia are 2-8% [2].

The infection of hepatitis B virus is often asymptomatic, so its development can be found after the virus infection develop into liver fibrosis, liver cirrhosis or hepatocellular carcinoma [3]. The liver fibrosis is a reversible process which is marked by over accumulated extracellular matrix (ECM) protein. Chronic liver injury causes the rise of ECM protein synthesis (fibrogenesis) and the degradation ECM protein (fibrolysis) [4]. The rise of fibrogenesis causes the blood perfusion in the liver disturbed. Hematopoietic stem cell (HSC) is a cell that is very important for liver fibrogenesis process. The injury in the liver cell causes the rise of the proliferation myofibroblast and ECM production, as well as the sedimentation of ECM component that cause ECM accumulation. Through this scientific theory, the stress of the HSC activity becomes important against liver fibrosis.

Liver fibrosis is a healing respond of liver tissue damage, which is reversible, and its development still can be blocked. Hence, liver fibrosis diagnostic is very important to be known earlier to begin the healing therapy of liver tissue injury [5]. The difficulty of liver fibrosis diagnostic makes there is no accurate data about the liver fibrosis occurrence in Prof. Dr. Margono Soekardjo Purwokerto General Hospital, Indonesia.

Liver biopsy is a standard liver fibrosis diagnostic. Nonetheless, liver biopsy has many weaknesses, for example, it can cause pain and bleeding, the possibilities of error in taking a sample, and the expensive cost needed to pay [6], hence liver biopsy has not used anymore in Prof. Dr. Margono Soekardjo Purwokerto General Hospital, Indonesia. Therefore, non-invasive method is developed to find the rate of liver fibrosis occurrence on the hepatitis B patients, such as using aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score, Fib-4, AST-alanine aminotransferase (ALT) ratio (AAR), age-platelet (AP) index and Pohl score.

The development of hepatitis B virus infection into a chronic liver injury generally takes time between 10 and 20 years [3]. However, its development can be faster by using hepatotoxic drug therapy that is a drug with ≥50% metabolism in the liver. Those drugs significantly cause 35% fatal liver injury, 28% liver failure, and 23% liver injury [7].

Therefore, this research will measure the non invasive liver fibrosis marker to find out the prevalence of liver fibrosis occurrence, and to evaluate the use of hepatotoxic drug at hepatitis B patients in Prof. Dr. Margono Soekardjo Purwokerto General Hospital, Indonesia.

METHODS

This research is retrospective and the data were taken by total sampling with descriptive qualitative and quantitative analysis. The source of data was medical records of hepatitis B patients from Prof. Dr. Margono Soekarjo Purwokerto General Hospital from January 2012 to August 2013, which covered age, gender, medical diagnostic, medicine prescription, AST level, ALT level, and platelet count.

The inclusion criteria in this research are hepatitis B patients with laboratory data of AST level, ALT level, platelet count and prescription data. Meanwhile, the exclusion criteria cover: (1) Liver cirrhosis patients, (2) hepatocellular carcinoma patients, (3) idiopathic thrombocytopenic purpura patients, (4) bleeding patients. The research sample who fulfilled all the criteria is 25 patients of hepatitis B from January 2012 to August 2013.

The formula of noninvasive fibrosis markers is calculated below: APRI = (AST/ULN)/Platelet ($\times 10^9$/L) × 100; Fib-4 = age (year) × AST (u/L)/(Platelet [$\times 10^9$/L] × (ALT [u/L]$^{1/2}$); AAR = AST/ALT; AP index = age + platelet (age: <30 = 0; 30-39 = 1; 40-49 = 2; 50-59 = 3; 60-69 = 4; ≥70 = 50, platelet [$\times 10^9$/L]: ≥225 = 0; 200-224 = 1; 175-199 = 2; 150-174 = 3; 125-149 = 4; < 125 = 5); and Pohl score that show positive fibrosis occurrence if AAR ≥1 and total platelet <150 × 10^9/L.

The use of hepatotoxic drug is known based on ≥50% metabolism in the liver, which can be found in Drug Information Handbook, Micromedex Drug Information, and AHFS Drug Information.

RESULTS AND DISCUSSION

Characteristic of hepatitis B patients

The result showed there were 25 patients who fulfilled the inclusion and exclusion criteria from January 2012 until August 2013. The average age of the 25 patients was 45.12±12.82, with age range 20-68 years old, 16 (64%) patients were men. The average of AST and ALT level showed that the average level is higher than their normal level, 15-37 u/L for AST and 30-65 u/L for ALT. The average level of ALT was 287.4±443.13 with ALT range 8-1.950 u/L. Meanwhile, the average of platelet count in hepatitis B patients sample was 180±117.3 ranging from 35 to 456 $\times 10^9$/L. The characteristic of hepatitis B patients can be seen in the Table 1.

Prevalence of liver fibrosis based on non-invasive markers APRI, AAR, FIB-4, AP index and Pohl score

The result showed that based on non-invasive markers APRI, AAR, FIB-4, and AP index, almost all of hepatitis B patients had fibrosis and cirrhosis. However, based on Pohl score, some patients had not yet had a liver fibrosis. Based on the data, it can be concluded that the prevalence of liver fibrosis in every non-invasive markers was different. The compilation of non-invasive markers is shown in Table 2.

Based on Fib-4 score, significant fibrosis can be found in 11 (44%) patients, and 8 (32%) patients did not have fibrosis. Based on APRI score, there were 5 (20%) patients who did not have fibrosis, 2 (8%) patients had significant fibrosis, and 12 (52%) patients had cirrhosis. AAR score showed that 15 (60%) patients had significant fibrosis, and 10 (40%) patients did not have fibrosis. Based on AP index, 13 (52%) patients had significant fibrosis and 12 (48%) patients did not have fibrosis, and based on Pohl score, significant fibrosis only can be found in 7 (28%) patients and the rest of them, or 18 (72%) patients did not have fibrosis. The result of non-invasive markers APRI, AAR, FIB-4, AP index, and Pohl score can be seen in Table 3.

Table 1: Characteristic of hepatitis B patients

	Hepatitis B patients (n=25)
Age (mean±SD, median, range [year])	45.12±12.82, 48, 20-68
Sex (%)	
Men	16 (64)
Women	9 (36)
AST (mean±SD, median, range [u/L])	202.44±306.05, 113, 15-1546
ALT (mean±SD, median, range [u/L])	287.4±443.13, 111, 8-1950
Platelet (mean±SD, median, range [$\times 10^9$/L])	180±117.3, 160, 35-456

SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

The difference in every non-invasive marker can be caused by the difference in pathology of the diseases in every patient that could influence the ability of non-invasive marker to assess the incidence of liver fibrosis [8]. Pathogenesis of liver fibrosis is related with every etiology and factor that cause the liver injury [9,10]. The differences in pathology of the diseases include kinds of virus, alcohol consumption, fat, sickness duration, complication, lifestyle, drugs use, and even a genetic factor. The laboratory data are expected to be non-invasive marker of fibrosis even though it includes non-direct marking.

Many studies have tried to validate externally the result of the non-invasive liver fibrosis marker, but the results are controversial. Vallet-Pichard et al., in their research showed that Fib-4 score had 98.2% specificity and 37.6% sensitivity in predicting the occurrence of significant liver fibrosis [11]. Shin et al. in their research showed that in predicting liver fibrosis, APRI had AUROC 0.86, which showed that APRI has high accuracy level to predict liver fibrosis [12]. Based on the article review that was done by Baranova et al., APRI had 89% sensitivity and 75% specificity to predict liver fibrosis [6]. Giannini et al. in their research showed that AAR had 73.7% sensitivity and 65% specificity to predict liver fibrosis [13]. Poynard and Bedossa's research showed that AP index had 93% specificity and 52% sensitivity [14]. Meanwhile, Cheung et al., in their research showed that in predicting liver fibrosis, Pohl score had AUROC 0.534 [15].

The infection development of hepatitis B virus into a chronic liver injury takes time between 10 and 20 years [3]. However, its development can be faster by using hepatotoxic drug therapy. This study showed the significant use of hepatotoxic drug. The use of hepatotoxic drug for hepatitis B patients' needs risk and benefits consideration. If the hepatotoxic drug is really important, there must be a special observation with its side effect that may occur, and the parameter of liver function to alleviate the risk of hepatotoxicity in patients. Besides, the accurate dose of the drug is very needed for the patients. This is because of the use of hepatotoxic drug with significant hepatic metabolism ≥50% can cause ALT >3 times upper limit of normal, fatal liver injury, liver failure, and liver transplantation [7].

Hepatotoxic drug that most widely used was ranitidine with 60% (Table 4). Hepatotoxic effect in ranitidine comes because ranitidine has first passed metabolism in the liver in a huge amount [16]. Liver injury is manifested by the increasing level of aminotransferase serum, alkaline phosphatase (ALP), lactate dehydrogenase, bilirubin, gamma-glutamyl transferase, and hepatic infiltration by limfosit and eosinophil, and it is also related to reversible fatal liver injury or cholestatic [16-19].

Liver injury that caused by hepatotoxic drug, for example, are acute liver injury, acute fatty infiltration, cholestatic jaundice, liver granulomas, active chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma [20]. Hepatocellular injury includes the increase of the aminotransferase serum, which mostly started by the increase of the high amount of bilirubin and a few increase of ALP serum. Cholestatic liver injury is marked by the increasing level of ALP serum higher than AST and ALT [21].

Every hepatitis B patients got hepatotoxic drug with a different amount; the amount of hepatotoxic drug in every patient can worsen the patient's condition. Based on Table 5, mostly the patients received one kind of hepatotoxic drug that was about 12 (48%) patients, whereas the patients that used hepatotoxic drug with the largest amount, that is 5 kinds of drug, were 1 (4%) patient.

CONCLUSION

Our study found that there was liver fibrosis that was found in hepatitis B patients based on APRI, Fib-4, AAR, AP index and Pohl score. In addition, it is also found that hepatotoxic drug is used by the hepatitis B patients.

Table 2: The compilation of non-invasive markers

No	Age (year)	Diagnosis	Laboratory data			Fib-4	APRI	AAR	AP index	Pohl
			AST (u/L)	Platelet (×10^9/L)	ALT (u/L)					
1	55	Hepatitis B	99	46	83	12.99 SF	5.82 C	1.19 SF	8 SF	F
2	68	Hepatitis B	341	193	520	5.26 SF	4.78 C	0.66 N	6 SF	N
3	41	Hepatitis B	230	180	217	3.55 SF	3.45 C	1.06 SF	4 N	N
4	21	Hepatitis B	408	192	1122	1.33 N	5.74 C	0.36 N	2 N	N
5	67	Hepatitis B	203	152	196	6.39 SF	3.61 C	1.04 SF	7 SF	N
6	20	Hepatitis B	163	314	578	0.43 N	1.4 NSF	0.28 N	0 N	N
7	48	Hepatitis B	78	259	61	1.85 NSF	0.81 NSF	1.28 SF	2 N	N
8	51	Hepatitis B	75	130	82	3.24 NSF	1.56 SF	0.91 N	7 SF	N
9	48	Hepatitis B	193	239	196	2.76 NSF	2.18 C	0.98 N	2 N	N
10	29	Hepatitis B	255	73.2	476	4.63 SF	9.41 C	0.54 N	5 N	N
11	52	Hepatitis B	1546	42	1950	43.34 SF	99.49 C	0.79 N	8 SF	N
12	55	Hepatitis B	39	54	37	0.12 N	1.95 SF	1.05 SF	8 SF	F
13	55	Hepatitis B	296	160	137	8.75 SF	5 C	2.16 SF	7 SF	N
14	51	Hepatitis B	182	80	148	9.53 SF	6.41 C	1.23 SF	8 SF	F
15	51	Hepatitis B	23	91	14	3.44 SF	0.68 NSF	1.64 SF	8 SF	F
16	45	Hepatitis B	65	35	51	11.7 SF	5.02 C	1.27 SF	7 SF	F
17	36	Hepatitis B	113	61	111	63.29 SF	5.01 C	1.02 SF	6 SF	F
18	36	Hepatitis B	437	82	788	6.83 SF	14.4 C	0.55 N	6 SF	N
19	41	Hepatitis B	85	282	68	1.49 NSF	0.81 NSF	1.25 SF	2 N	N
20	55	Hepatitis B	24	140	21	2.05 NSF	0.46 N	1.14 SF	7 SF	F
21	36	Hepatitis B	33	265	21	0.97 N	0.34 N	1.57 SF	1 N	N
22	28	Hepatitis B	21	387	44	0.22 N	0.15 N	0.48 N	0 N	N
23	61	Hepatitis B	15	225	8	1.43 N	0.18 N	1.88 SF	4 N	N
24	37	Hepatitis B	16	357	15	0.42 N	0.12 N	1.07 SF	1 N	N
25	41	Hepatitis B	121	456	241	0.7 N	0.72 NSF	0.5 N	2 N	N

N: Normal, NSF: Not significant fibrosis, SF: Significant fibrosis, C: Cirrhosis, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, APRI: AST-to-platelet ratio index, AAR: AST-ALT ratio, AP: Age-platelet

Table 3: The number of patients in each non-invasive fibrosis markers

Non-invasive marker	Stage of liver fibrosis (n=25) (%)			
	Normal	Not significant fibrosis	Significant fibrosis	Cirrhosis
Fib-4	8 (32)	6 (24)	11 (44)	-
APRI	5 (20)	5 (20)	2 (8)	13 (52)
AAR	10 (40)	-	15 (60)	-
AP index	12 (48)	-	13 (52)	-
Pohl	18 (72)	-	7 (28)	-

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, APRI: AST-to-platelet ratio index, AAR: AST-ALT ratio, AP: Age-platelet

Table 4: The distribution of the use of hepatotoxic drug on the hepatitis B patients

Drug name	∑ patients (n=25)	Percentage
Ranitidine	15	60
Spironolactone	8	32
Omeprazole	5	20
Ondansetron	5	20
Propranolol	4	16
Acetaminophen	2	8
Amlodipine	2	8
Pantoprazole	1	4
Metronidazole	1	4
Isosorbide dinitrate	1	4
Tamoxifen	1	4
Diazepam	1	4

Table 5: The distribution of the hepatitis B patients who got hepatotoxic drug

∑ hepatotoxic drug	∑ patients (n=25)	Percentage
5	1	4
4	3	12
3	1	4
2	7	28
1	12	48
0	1	4

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