Liver fibrosis of hepatitis C virus infection in routine hemodialysis patients in Indonesia

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ABSTRACT

BACKGROUND The risk of hepatitis C virus (HCV) infection is increasing in patients under routine hemodialysis, but only some patients progress to liver fibrosis. This study was aimed to identify the prevalence of significant liver fibrosis in routine hemodialysis patients with hepatitis C infection as well as factors associated with liver fibrosis.

METHODS This cross-sectional study was conducted in three tertiary general hospitals (Cipto Mangunkusumo Hospital, Persahabatan Hospital, and Fatmawati Hospital) in Jakarta, Indonesia, among hemodialysis patients infected with HCV. Total sampling was used from May to September 2017 in hemodialysis unit of all hospitals. Sex, age, time at first diagnosis of HCV, duration of HCV infection, duration of hemodialysis, AST level, hepatitis B virus coinfection and diabetes mellitus were analyzed in association with significant liver fibrosis. Liver fibrosis was assessed using transient elastography and considered significant if the value was ≥7.1 kPa. Chi-square, Mann–Whitney *U*, and Fisher's exact tests were used. Risk model was analyzed with logistic regression.

RESULTS Of the 133 hemodialysis patients infected with HCV, 71.4% of the subjects had significant liver fibrosis. In the risk model, male gender (odds ratio [OR] = 3.92; 95% confidence interval [CI] = 1.74–8.84; $p < 0.001$) and diabetes mellitus (DM) (OR = 2.85; 95% CI = 1.03–7.88; $p = 0.043$) were associated with significant liver fibrosis.

CONCLUSIONS The prevalence of significant liver fibrosis in routine hemodialysis patients with hepatitis C infection was high. Male and DM were associated with significant liver fibrosis.

KEYWORDS hemodialysis, hepatitis C, liver fibrosis

Liver fibrosis is a chronic progressive liver damage characterized by the accumulation of extracellular matrix, which can lead to changes in liver architectures and ultimately develop into cirrhotic nodules.[1,2] Patients with advanced liver fibrosis are at risk of having hepatocellular carcinoma with a rate of 1–2% per year.[3] Fibrosis is considered significant when there is fibrosis with septa. This significant fibrosis is shown as fibrosis F2 by transient elastography.[4]

Hepatitis C is the most common cause of liver fibrosis, and its prevalence in hemodialysis patients varies from 4 to 60% worldwide.[5–7] A meta-analysis conducted by Fabrizi et al,[8] demonstrated positive hepatitis C virus (HCV) infection is a risk factor for mortality in hemodialysis patients with a relative risk of 1.35.[9] Hemodialysis patients with HCV infection in Indonesia usually do not receive treatment, and data on the progression to liver cirrhosis have not been documented. HCV infection may also result in extrahepatic clinical manifestations, including cardiovascular, cerebrovascular, renal, and endocrine.[10] The high HCV infection prevalence among hemodialysis

patients and the fact that HCV infection contributes to a higher mortality rate in such patients mandate extra attention in this particular topic.

The greater degree of liver fibrosis is associated with progression to liver cirrhosis and death. Evaluation of liver fibrosis in HCV infection may have a role in the management and treatment plan. Transient elastography (TE) or FibroScan® is a noninvasive, easy, and rapid method to evaluate the degree of liver fibrosis. Kidney Disease Improving Global Outcomes (KDIGO) recommended liver fibrosis evaluation for patients with HCV infection to treatment initiation, liver fibrosis monitoring, and evaluation of possibility for kidney transplantation.[11] Some studies have been conducted to evaluate factors associated with liver fibrosis in patients with HCV infection who did not undergo hemodialysis. The factors include age >40 years at the time of infection, male gender, duration of HCV infection, concomitant infection with hepatitis B, diabetes mellitus (DM), and high transaminase level.[12–15] However, only several studies have evaluated this issue in hemodialysis patients, and the result are varied.[16] In Indonesia, no reports have yet documented regarding liver fibrosis in hemodialysis patients with HCV coinfection. Therefore, this study is aimed to evaluate the prevalence of significant liver fibrosis in hemodialysis patients with HCV infection and factors associated with the development of liver fibrosis.

METHODS

This was a cross-sectional study in routine hemodialysis patients infected with HCV at the Hemodialysis Unit of Cipto Mangunkusumo Hospital, Persahabatan Hospital, and Fatmawati Hospital in Jakarta, Indonesia from May to September 2017. This study has been approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No: 632/UN2.F1/ETIK/2017).

Subjects were recruited using total population sampling in all hemodialysis unit of three hospitals. There were 402 patients underwent routine hemodialysis in three hospitals (192 patients in Cipto Mangunkusumo Hospital, 90 patients in Persahabatan Hospital, 120 patients in Fatmawati Hospital) and the subjects were recruited based on anti-HCV positivity from medical record. The exclusion criteria were patients with any previous HCV treatment or HIV coinfection. All patients gave written consent, and subsequently, history taking and physical examination were performed. Transient elastography examination was carried out to identify significant (≥7.1 kPa, F2–F4) and nonsignificant (<7.1 kPa, F0–F1) liver fibrosis. All subjects were grouped based on sex, age at HCV infection (below or over the age of 40 years), duration of HCV infection (less or more than 10 years), duration of hemodialysis therapy, aspartate aminotransferase (AST) level, concomitant hepatitis B infection (with or without infection), and DM.

Statistical analysis

Statistical analyses were done using SPSS software version 20 (IBM Corp, USA). Chi-square test was used to analyze the association between significant liver fibrosis and DM, age at HCV infection, duration of hemodialysis therapy. Fisher's exact test was used to analyze the association between sex, hepatitis B infection and significant liver fibrosis. Odds ratios (OR) were also calculated between variables. Mann–Whitney *U* test was used to analyze the association between AST level and significant liver fibrosis. A multivariate analysis using logistic regression was carried out to identify risk factors associated with significant liver fibrosis. All independent variables that have a *p*-value <0.25 in the bivariate analysis were entered into the logistic regression model. A *p*-value of <0.05 was considered statistical significance.

RESULTS

Of the 402 patients who had undergone hemodialysis, there were 156 patients infected with HCV in Cipto Mangunkusumo Hospital (n = 77), Persahabatan Hospital (n = 50), and Fatmawati Hospital (n = 27). However, 14 patients refused to participate in the study, 5 patients were not eligible for examination due to ascites and 4 patients died. No patient with HIV coinfection and previous history of HCV treatment was found. Thus, the study included 133 subjects. The mean (standard deviation [SD]) of age was 51.04 (12.9) years, and 75 (56.4%) subjects were men.

In the three hospitals, this study showed that as many as 95 of 133 subjects (71.4%; 95% CI = 63.74–79.06) had significant liver fibrosis. The characteristics of the subjects can be seen in Table 1.

Sex, age at infection, AST level were associated with significant liver fibrosis in bivariate analysis (Table 2). In multivariate analysis, only sex and DM

Table 1. Subject characteristics

Variables	n (%) (N = 133)
Male sex	75 (56.4)
Age (years), mean (SD)	51.04 (12.982)
BMI (kg/m^2), median (min–max)	21.83 (14.04–34.77)
Moment of HCV infection diagnosis	
Before having hemodialysis	8 (6)
After having hemodialysis	125 (94)
Age at hepatitis C diagnosis (years)	
<40	36 (27.1)
≥40	97 (72.9)
Duration of HCV infection (months), median (min–max)	18 (0–108)
Duration of hemodialysis therapy (years)	
<10	111 (83.4)
≥10	22 (16.5)
AST level (U/l), median (min–max)	25 (6–177)
Concomitant hepatitis B infection	8 (6)
DM	36 (27.1)
Duration of DM (years), mean (SD)	13.26 (6.4)
Degree of liver fibrosis	
<7.1 kPa (nonsignificant)	38 (28.6)
≥7.1 kPa (significant)	95 (71.4)

SD=standard deviation; BMI=body mass index; HCV=hepatitis C virus; AST=aspartate aminotransferase; DM=diabetes mellitus

became independent risk factors for significant liver fibrosis in patients with HCV infection who undergone hemodialysis (Table 2).

DISCUSSION

This study found 71.4% of routine hemodialysis patients infected with HCV had significant liver fibrosis. On the contrary, a study by Becker et al[16] in Brazil showed only 23% of patients had significant fibrosis. A retrospective cohort study by Agarwal and Gupta[17] in India, which was carried out between 1995 and 2015 showed that among 277 hepatitis C cases, 13.6% subjects had significant fibrosis. The differences may be resulted from younger age (34.05 [10.28] years old) and shorter duration of HCV infection (5.2 [4.0] months) in study from India.[17]

A previous study showed that male was an independent risk factor for the progression of liver fibrosis in patients with HCV infection who have normal renal function.[18] That study also revealed male as risk factor for liver fibrosis (OR = 3.924; 95% CI = 1.741–8.842; $p < 0.001$) among hemodialysis patients coinfected with HCV.[18] Our study also showed similar result. The higher risk of developing liver fibrosis in patient with HCV infection. Shimizu et al[19] reported that estradiol at physiological doses suppressed the development of hepatic fibrosis both *in vitro* and *in vivo* models by inhibiting a collagen production, reducing an α-smooth muscle actin (α-SMA) expression, and reducing an intermediate filament expression called desmin. Both α-SMA and desmin are expressed by myofibroblast-like cells that originated from activated stellate cells. It also found that estradiol inhibits activated stellate cell spreading and DNA synthesis. The findings suggested that estradiol is a potent inhibitor of stellate cell transformation and thus plays some antifibrogenic role in the liver.[19]

The multivariate analysis showed that age at diagnosis of more than 40 years was not associated with higher risk of fibrosis progression. On the contrary, the study by Becker et al[16] demonstrated that an estimated age at diagnosis of >40 years is an independent risk factor of liver fibrosis. Such differences may be related to different subject characteristics; Becker et al[16] recruited younger subjects (36 [11] years old) than this study (51 [13] years), and it was difficult to accurately determine the age at hepatitis C diagnosis. Age at diagnosis generates the same effect on liver fibrosis in patients with chronic kidney disease and nonuremic individuals. A hypothesis has been proposed that the capacity of the immune system to overcome the pathological effects of hepatitis C is diminished with age.[16] Moreover, it also has been demonstrated that age at the time of infection of over 40 years showed a higher proportion of significant liver fibrosis compared with those under 40 years of age.

There was also no evidence of higher risk of liver fibrosis progression between the duration of hepatitis C diagnosis and significant liver fibrosis in patients undergoing hemodialysis; the median in this study was 18 months. Dienstag et al[14] with different population (patients with normal renal function). Santoro et al[20] showed that anti-HCV positive patients who had been diagnosed showed that the duration of having hepatitis C infection was associated to liver fibrosis with a mean duration of 17.5 years with liver fibrosis had a median of 10 years (4–16 years) since they started hemodialysis treatment.

Table 2. Bivariate and multivariate analyses of factors associated with significant liver fibrosis

Variables	Significant fibrosis, n (%) (N = 95)	Nonsignificant fibrosis, n (%) (N = 38)	Bivariate analysis		Multivariate analysis	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Male sex	62 (65.3)	13 (34.2)	3.613 (1.636–7.978)	**0.001***	3.924 (1.741–8.842)	**0.001**
Age at hepatitis C infection (years)						
<40	21 (22.1)	15 (39.5)	1.00		1.00	
≥40	74 (77.9)	23 (60.5)	2.298 (1.021–5.172)	**0.042**†	0.452 (0.149–1.376)	0.162
Duration of hepatitis C infection (months), median (min–max)	18 (0–108)	18 (3–81)	-	-	0.686‡	
Duration of hemodialysis therapy (years)						
<10	78 (82.1)	33 (86.8)	0.695 (0.237–2.041)	0.507†		
≥10	17 (17.9)	5 (13.2)	1.00			
AST level (U/l), median (min–max)	28 (6–177)	18 (6–130)	-	-	**0.012**‡	0.982 (0.959–1.005)	0.128
Concomitant hepatitis B infection	7 (7.4)	1 (2.6)	2.943 (0.350–24.771)	0.439*		
DM	30 (31.6)	6 (15.8)	2.462 (0.930–6.515)	0.064†	2.854 (1.034–7.879)	**0.043**

OR=odds ratio; CI=confidence interval; AST=aspartate aminotransferase; DM=diabetes mellitus
*Fisher's exact test; †Chi-square test; ‡Mann–Whitney *U* test

No association between the duration of hemodialysis therapy and significant liver fibrosis may be because HCV has mild activity and it is not progressive in hemodialysis patients, which may be due to the immunological nature of those patients.[21] This study showed that AST level did not have higher risk of liver fibrosis. AST was found to have an independent association with liver fibrosis in patients with uremia.[16] In comparison with this study, the subjects included by Becker et al[16] had a higher AST level, which may affect the results. AST may serve as a predictor of liver fibrosis in hemodialysis patients. Moreover, patients with a higher AST level must have strict monitoring since it may suggest more severe liver damage.[16]

Concomitant infection with hepatitis B was not shown to have higher risk of liver fibrosis in hepatitis C patient who had undergone hemodialysis (p = 0.439). The small number of subjects with hepatitis B in this study (n = 8) might be the reason for the nonsignificant result. Previous studies in patients with normal renal function conducted by Sagnelli et al[22] and Caccamo et al,[23] concomitant infection of hepatitis B and hepatitis C has higher risk of more severe histological liver abnormalities.

It has been demonstrated that DM has higher risk of liver fibrosis in hemodialysis patient with HCV infection (p = 0.043). A study by Huang et al[24] in a general population has shown that DM is an independent risk factor for cirrhosis. DM in patients with hepatitis C infection accelerates the progression of fibrosis into cirrhosis and hepatocellular carcinoma, since from the pathogenesis point of view, it may cause liver steatosis. Diminished insulin sensitivity that occurs in DM may also increase the release of free fatty acid from the adipose tissues, and it may increase lipid hepatic deposition.[15]

Although this study was aimed to determine the prevalence of liver fibrosis in hemodialysis patients, it was revealed that the prevalence of hepatitis C is high in the three hospitals studied. The Indonesian Society of Nephrology issued a recommendation in 2006 to control the nosocomial transmission of HCV infection in hemodialysis units. Nowadays, the process of reusing dialyzer is carried out using separate machines. In the past, it was performed manually with formaldehyde without the use of automated equipment. Other factors considered to contribute to the decreasing prevalence of HCV infection is the increasing use of erythropoietin (EPO). The use of EPO

decreases the need for a blood transfusion, which may eventually decrease the risk of transmission of HCV infection. A multicenter study at a hemodialysis unit showed that the incidence of hepatitis seroconversion had been reduced from 1.41% to 0% only per year by performing greater efforts on strict enforcement of universal precautions.[25] It indicates that good practice of universal precaution can prevent the nosocomial transmission of HCV infection in the hemodialysis unit and that the isolation of anti-HCV positive patients is not necessary.

However, this study has some limitations. First, this cross-sectional study may demonstrate weak evidence of a causal relationship between the variables studied. Second, it is difficult to know accurately when an HCV infection is diagnosed since it is asymptomatic; therefore, variables of the duration of HCV infection in this study was based on laboratory reports.

Based on this study, it can be concluded that the prevalence of significant liver fibrosis among hemodialysis patients with hepatitis C at the Hemodialysis Unit in Cipto Mangunkusumo Hospital, Persahabatan Hospital, and Fatmawati Hospital in was found in 71.4%. Male and DM were associated with significant liver fibrosis. Meanwhile, age at hepatitis C diagnosis, duration of hepatitis C infection, duration of hemodialysis, AST level, and concomitant hepatitis B infection did not show any association with significant liver fibrosis in this study.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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