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CLINICAL STUDY

Non-alcoholic fatty liver disease increases the prevalence of maintenance haemodialysis in patients with chronic kidney disease

Lu YC[1], Hsu CY[2,3,4,5,6,7,8,9,10]

Department of Family Medicine, Puli Christian Hospital, Puli, Taiwan. **4211@mail.pch.org.tw**

ABSTRACT

AIM: To investigate the association between non-alcoholic fatty liver disease (NAFLD) and incidence of maintenance haemodialysis in patients with chronic kidney disease (CKD).

METHODS: We enrolled patients diagnosed with CKD between 2001 and 2007. The patients were categorized into two groups based on abdominal ultrasound finding, namely those with NAFLD and those without NAFLD. The disease (maintenance haemodialysis)-free survival rate was estimated using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses was used to evaluate the hazard ratios of covariates for the incidence of maintenance haemodialysis.

RESULTS: A total of 161 patients (61 with NAFLD and 100 without NAFLD) were enrolled. The mean age was 69.3 years. The mean follow-up was 7.4 years. The patients with NAFLD had an increased incidence of maintenance haemodialysis (39.3 % vs 24.0 %; p=0.0396) and inferior disease-free survival rate (p=0.006). Furthermore, diabetes (p=0.0126) and proteinuria (p=0.0003) were identified as significant predictors of CKD progression.

CONCLUSION: NAFLD was associated with an increased incidence of maintenance haemodialysis and inferior disease-free survival rate. NAFLD may impair renal function and patients with renal impairment should be monitored carefully *(Tab. 3, Fig. 1, Ref. 25)*. Text in PDF *www.elis.sk.*

KEY WORDS: non-alcoholic fatty liver disease, haemodialysis, chronic kidney disease, proteinuria.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in western countries, affecting 25–30 % of the population (1, 2). In Asia, the prevalence of NAFLD varies from 5 to 30 % (3), and NAFLD is characterized by fat infiltration of the liver without significant alcohol consumption, use of medication, or other medical problems (4). NAFLD and non-alcoholic steatohepatitis are two pathologically distinct conditions with different NAFLD prognoses. While the latter is recognized as the leading cause of fibrosis, cirrhosis and hepatocellular carcinoma (5), NAFLD is confined not only to progressive liver disease, it also affects other major extra-hepatic organs and regulatory pathways (6, 7).

Chronic kidney disease (CKD) is an emerging global public health problem resulting in high morbidity, mortality and health care burden (8). According to the 2017 United States Renal Data System annual data report, the prevalence of end-stage renal disease (ESRD) was 3,317 per million people in Taiwan, which was the highest national rate worldwide, and this number continues to rise. Accordingly, early prevention and identification of ESRD are vital for reducing the burden of healthcare expenditure.

Several recent studies have demonstrated that NAFLD (diagnosed using biochemistry, non-invasive scoring system, or ultrasonography) is associated with increased prevalence of CKD (9–14). The largest and most up-to-date meta-analysis (nine observational studies with 96,595 participants) revealed that a nearly 40% increase in long-term risk of CKD was conferred in NAFLD (15). To our knowledge, no study has investigated the effect of NAFLD on CKD progression. Therefore, the present retrospective study determined the association between NAFLD and incidence of maintenance haemodialysis in patients with CKD.

[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [2]Department of Family Medicine, Puli Christian Hospital, Puli, Taiwan, [3]Department of Medical Education and Research, Puli Christian Hospital, Puli, Taiwan, [4]Department of Optometry, Central Taiwan University of Science and Technology, Taichung, Taiwan, [5]Center for General Education, National Taichung University of Science and Technology, Taichung, Taiwan, [6]The General Education Center, Chaoyang University of Technology, Taichung, Taiwan, [7]Department of General Education, National Chin-Yi University of Technology, Taichung, Taiwan, [8]Center for General Education, Feng Chia University, Taichung, Taiwan, [9]National Chi Nan University, Puli, Taiwan, and [10]Rural Generalist Program Japan

Address for correspondence: Chao-Yu Hsu, Tie-Shan Road 1, Puli, Nantou 545, Taiwan
Phone: +886.492912151, Fax: +886.492916901

Materials and methods

We enrolled patients diagnosed with CKD between 2001 and 2007 (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 585.0). The patients were enrolled based on the following criteria: (a) serum creatinine > 1.0 mg/dL, (b) at least one abdominal ultrasound before enrolment or in the subsequent 2 years, and (c) at least 3 years' follow-up. We excluded patients who (a) had alcohol abuse or alcoholic hepatitis, (b) had history of liver cirrhosis or other liver disease, (c) were positive for hepatitis B surface antigen or hepatitis C virus antibody, (d) had evidence of malignancy, (e) had an estimated glomerular filtration rate (eGFR) of < 15 mL/min/1.73 m^2, or (f) underwent maintenance haemodialysis in the subsequent 3 years.

The data were obtained from the database of our hospital, inclusive of demographic characteristics and medical history. Abdominal ultrasound was performed by experienced specialists. Hyperlipidaemia was defined as triglyceride levels of ≥ 150 mg/dL, low-density lipoprotein cholesterol levels of ≥ 200 mg/dL, or use of medication for dyslipidaemia. The variables for analysis included serum creatinine, aspartate transaminase, alanine transaminase, platelets, uric acid, and urine protein levels. One study indicated that fibrosis-4 (FIB-4) is an effective predictor of CKD among non-invasive systems for scoring NAFLD (16). Therefore, FIB-4 was recorded. In addition, eGFR was calculated by the Modification of Diet in Renal Disease equation. The endpoint of this study was the initiation of maintenance haemodialysis, and the date of haemodialysis commencement was recorded. The time of follow-up started when the participants met the eligible criteria and ended either when the endpoint occurred or on September 30, 2018.

Continuous variables were represented as mean ± standard deviation, and qualitative data were represented as numbers with percentages. Group comparisons among the characteristics of the study participants between different NAFLD statuses were evaluated as appropriate by using the t-test and chi-square test. The disease (maintenance haemodialysis)-free survival rate was estimated through the Kaplan-Meier survival analysis. In addition, we performed univariate and multivariate Cox regression analyses to evaluate the hazard ratios of covariates for the incidence of maintenance haemodialysis. A p value of < 0.05 was considered statistically significant.

Results

A total of 161 patients (61 with NAFLD and 100 without NAFLD) were enrolled in the final study. The baseline characteristics of the enrolled patients were stratified by the presence of NAFLD and summarized in Table 1. The mean age was 69.3 ± 11.0 years. The patients with NAFLD were more likely to be aboriginal and have diabetes, hyperlipidaemia or proteinuria. No differences in age, sex, hypertension, eGFR or other biochemical data were observed. FIB-4 exhibited no difference (Tab. 1).

Over the mean of 89.0 ± 35.1 months (7.4 ± 2.9 years) of follow-up, the patients with NAFLD exhibited a higher incidence

Tab. 1. Baseline characteristics of study patients by NAFLD status.

Variable	No NAFLD (n = 100)	NAFLD (n = 61)	P value
Age	69.5±10.5	68.9±11.8	0.7359
Sex			0.0527
Male	60 (60.0%)	27 (44.3%)	
Female	40 (40.0%)	34 (55.7%)	
Race			0.0337
Aborigine	5 (5.0%)	9 (14.8%)	
Non-aborigine	95 (95.0%)	52 (85.2%)	
Hypertension	75 (75.0%)	46 (75.4%)	0.9536
Diabetes	24 (24.0%)	29 (47.5%)	0.0021
Hyperlipidaemia	33 (33.0%)	32 (52.5%)	0.0149
Proteinuria	37 (37.0%)	33 (54.1%)	0.0343
Creatinine	1.82±0.60	1.74±0.54	0.4130
Estimated GFR	39.51±13.54	39.89±14.81	0.8695
Uric acid	8.05±2.30	7.57±2.34	0.2606
ALT	23.39±16.94	25.28±20.83	0.5656
AST	26.05±14.48	27.36±17.54	0.6401
Platelet	210.45±64.83	230.34±88.61	0.1376
FIB-4	2.06±1.01	1.99±1.25	0.7509

Values in the table are mean ± SD or number (%). NAFLD: non-alcoholic fatty liver disease; GFR: glomerular filtration rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FIB-4: fibrosis-4.

Tab. 2. Incidence rate and time up to the initiation of maintenance haemodialysis.

	No NAFLD (n = 100)	NAFLD (n = 61)	p-value
Haemodialysis	24 (24.0%)	24 (39.3%)	0.0396
Time up to the initiation of haemodialysis (months)	94.5±32.7	83.5±37.2	0.2842

Values in the table are mean ± SD or number (%).

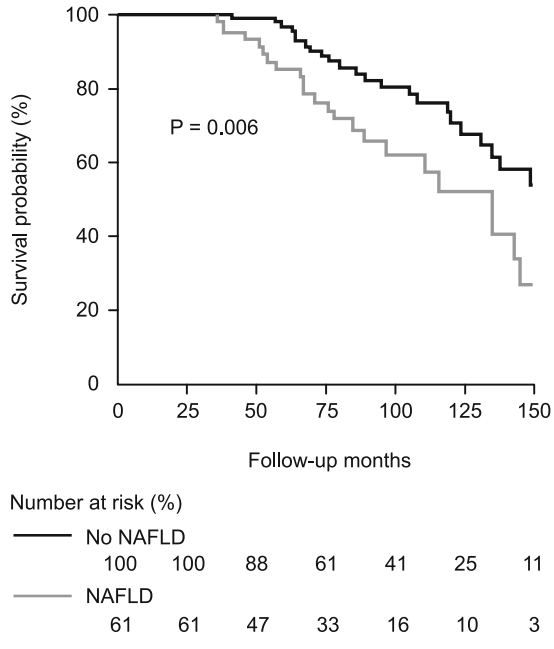

Fig. 1. Survival curve of incidence of maintenance haemodialysis by NAFLD status.

Tab. 3. Univariate and multivariate Cox regression analyses.

Covariates	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.99 (0.96-1.02)	0.4257	0.93 (0.85-1.02)	0.1038
Gender	0.50 (0.28-0.89)	0.0192	0.59 (0.19-1.77)	0.3419
Race	1.97 (0.83-4.71)	0.1258	0.54 (0.11-2.55)	0.4329
Hypertension	1.41 (0.68-2.92)	0.3513	3.38 (0.92-12.39)	0.0659
Diabetes	2.55 (1.41-4.60)	0.0019	4.75 (1.40-16.18)	0.0126
Hyperlipidaemia	1.11 (0.63-1.96)	0.7184	0.59 (0.16-2.15)	0.4233
Proteinuria	4.12 (2.07-8.23)	0.0001	7.37 (2.47-21.95)	0.0003
Creatinine	2.27 (1.36-3.79)	0.0017	0.82 (0.16-4.16)	0.8152
Estimated GFR	0.96 (0.94-0.99)	0.0024	0.96 (0.89-1.03)	0.2310
Uric acid	0.76 (0.64-0.90)	0.0019	0.84 (0.66-1.07)	0.1646
ALT	0.99 (0.98-1.01)	0.6128	0.96 (0.90-1.02)	0.1620
AST	1.01 (0.99-1.03)	0.3858	1.06 (1.00-1.13)	0.0581
FIB-4	0.95 (0.66-1.36)	0.7671	1.23 (0.49-3.14)	0.6580

HR: hazard ratio; CI: confidence interval; NAFLD: non-alcoholic fatty liver disease; GFR: glomerular filtration rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FIB-4: fibrosis-4.

of maintenance haemodialysis than did those without NAFLD (39.3 % vs 24.0 %; p = 0.0396) (Tab. 2). The time up to the initiation of maintenance haemodialysis among the patients with NAFLD was shorter than among those without NAFLD, although no statistical significance was detected (83.5 ± 37.2 vs 94.5 ± 32.7; p = 0.2842). However, further evaluation through Kaplan-Meier analysis revealed a significantly inferior disease-free survival rate for patients with NAFLD (p = 0.006) (Fig. 1).

In univariate Cox regression analysis, sex, diabetes, proteinuria, creatinine, eGFR, and uric acid were significantly associated with increased rates of maintenance haemodialysis initiation. However, the multivariate Cox regression model revealed that only diabetes and proteinuria were significant independent predictors (Tab. 3).

Discussion

To our knowledge, this was the first retrospective cohort study to investigate the association between the presence of NAFLD and incidence of maintenance haemodialysis in patients with CKD. We demonstrated that patients with NAFLD had an increased incidence of maintenance haemodialysis and inferior disease-free survival rate compared with those without NAFLD. Furthermore, diabetes and proteinuria were identified as significant independent predictors associated with CKD progression in multivariate Cox regression analysis.

Although the previous studies have demonstrated male predominance in the NAFLD population, the exact mechanism is not comprehensively understood (6). However, the present retrospective study discovered that the prevalence of NAFLD in women was higher than that in men, which can be possibly explained by the fact that women have a higher percentage of essential body fat, or by the tendency of men to consume more alcohol (17), which in turn can result in alcoholic hepatitis – and that was an exclusion criterion in the present study.

In the present study, the prevlence rates of diabetes and hyperlipidaemia were higher in patients with NAFLD. The multivariate Cox regression analysis revealed that diabetes was an independent predictor of the initiation of maintenance haemodialysis. These findings were similar to those of previous studies that have revealed a bidirectional association between NAFLD and components of metabolic syndrome such as obesity, type 2 diabetes and hyperlipidaemia (6, 7). Furthermore, there is evidence indicating that the metabolic syndrome is associated with CKD development (18–20). Some studies have suggested that NAFLD increases systemic chronic inflammation and insulin resistance (21–23), which may explain the role of NAFLD in CKD progression.

Because previous studies have investigated the effect of NAFLD on CKD incidence, the patients with eGFR < 60 mL/min/1.73 m^2 or proteinuria have been excluded from such studies (9–12). In our study, which investigated the association of NAFLD and CKD progression, we included patients with eGFR > 15 mL/min/1.73 m^2, regardless of their proteinuria states. The results revealed that the patients with NAFLD had a higher proportion of proteinuria, which is an independent predictor of maintenance haemodialysis initiation.

The stage of fibrosis is the most crucial prognostic factor in NAFLD for predicting liver-related outcomes and mortality (24). The European Association for the Study of the Liver recommended evaluating fibrosis markers in patients with NAFLD (1). A recent study analysed the association between fibrosis markers and prevalence of CKD in patients with NAFLD, and demonstrated that FIB-4 is the most valid predictor for distinguishing patients with CKD compared with other non-invasive fibrosis markers (16). However, the present study observed no consistent correlation between FIB-4 and incidence of maintenance haemodialysis, possibly because FIB-4 is superior to ESRD in predicting CKD or because the study population was relatively small.

This was a retrospective study, and several limitations must be considered in the interpretation of our findings. Firstly, this was a single-centre study from a regional hospital in central Taiwan, and thus selection biases may have existed. Lifestyle preferences and ethnic composition differed between rural and urban areas. Secondly, NAFLD was defined based on abdominal ultrasound after excluding the competing liver aetiologies, rather than on liver biopsy. Although liver biopsy is the most reliable approach for diagnosing NAFLD, it is impractical in routine clinical practice because of its cost, sampling error, and procedure-related complications (5, 25). Thus, abdominal ultrasound remains the first-line procedure for diagnosing NAFLD in clinical practice. Thirdly, the ultrasound-based grading of NAFLD was lacking in the documentation. There may exist an association between NAFLD severity and CKD progression. Finally, detailed information on CKD pathology was unavailable, and thus we were unable to fully exclude other possible causes of CKD deterioration. Although several limitations affected this study, we determined that NAFLD increased the incidence of maintenance haemodialysis and lowered the disease-specific survival rate in patients with CKD.

Conclusion

NAFLD increased the incidence of maintenance haemodialysis and reduced the disease-free survival rate. NAFLD plays a role in CKD progression, and patients with renal impairment should be monitored carefully.

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