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Prevalence and Severity of Non-Alcoholic Fatty Liver Disease in Patients with Chronic Kidney Disease

Shaveta Dahiya, Varun Kulkarni**, Tarana Gupta***, Deepak Jain***, HK Aggarwal*****

Abstract

Introduction: *Recent studies have shown increased prevalence of NAFLD in CKD. The presence and severity of NAFLD has been related to the incidence and stage of CKD independently of traditional CKD risk factors. Further it is postulated that the pathogenic mechanisms causing steatosis and renal injury are common to both, such as insulin resistance, chronic systemic inflammation and dyslipidaemia.*

Objective: *We aimed to evaluate the prevalence of Nonalcoholic Fatty Liver Disease in patients of Chronic Kidney Disease and to determine the severity of Liver Fibrosis in different stages of Chronic Kidney Disease. We also compared efficacy of transient elastography with different fibrosis scores (NFS, FIB-4, APRI) in diagnosing liver fibrosis and estimating its severity.*

Material and methods: *All patients > 18 years with chronic kidney disease, not on renal replacement therapy reporting to Department of Medicine and Nephrology clinic were included into the study and subjected to USG of liver for presence of hepatic steatosis. 100 patients of CKD with evidence of hepatic steatosis on ultrasonography were enrolled into the study who further underwent transient elastography (TE) for determining the severity of liver fibrosis. Fibrosis scores: APRI, NAFLD fibrosis score and FIB-4 index were calculated and specific cut-off values were taken to categorise liver fibrosis into stages.*

Results: *Out of 140 patients of CKD who were screened, 100 patients were found to have evidence of fatty liver, which indicates a prevalence of 71.4%. Use of transient elastography suggested that in patients of stage 3 CKD (n = 24), 3(12.5%) patients had advanced fibrosis, 9 patients had fibrosis F_1-F_2 and 12 patients had no fibrosis. In patients of stage 4 CKD (n = 30), 11(36.6%) patients had advanced fibrosis, 8 patients had fibrosis F_1-F_2 stage and 11 patients had no fibrosis. In stage 5 CKD (n = 46), 33 (71.7%) patients had advanced fibrosis, 8 patients had fibrosis F_1-F_2 and 5 patients had no fibrosis. With increasing stage of CKD, the severity of liver fibrosis increased. Among all non-invasive markers when compared with transient elastography, NAFLD fibrosis score and FIB-4 Index could reliably predict advanced fibrosis in patients with CKD.*

Conclusion: *In our study, we found that NAFLD is significantly associated with CKD with high prevalence in this population. Further we found that advanced fibrosis is significantly more prevalent in advanced CKD stage 5 compared to CKD stages 3 and 4.*

Key words: *CKD, NAFLD, transient elastography, non-invasive scores.*

Introduction

Chronic kidney disease (CKD) is one of the leading causes of chronic diseases globally, with rising incidence and prevalence. The worldwide prevalence of CKD is estimated to be 10.4 - 13.4%[1]. The incidence and prevalence of CKD in India are approximately 0.16% and 0.78%, respectively[2]. Overall CKD mortality has increased by 31.7%, which makes it one of the fastest rising major causes of death[3]. The rising incidence of CKD reflects the rising incidence of obesity, diabetes mellitus (DM), hypertension and metabolic syndrome (MS). Non-alcoholic fatty liver disease (NAFLD) has been defined as accumulation of fat in the liver in the absence of significant alcohol intake, use of medications, or medical conditions that cause fatty liver. The definition also includes the exclusion of other secondary causes of fatty liver, such as presence of hepatitis B and C infection, drug and toxin exposure, surgical procedures, inborn errors of metabolism and total parenteral nutrition. NAFLD has a wide spectrum of disease ranging from 'Non-alcoholic fatty liver' (NAFL), Non-alcoholic steatohepatitis (NASH), NASH-related cirrhosis and NASH-related hepatocellular carcinoma (HCC). NASH is defined as steatosis and inflammation associated with ballooning of hepatocytes, presence of Mallory hyaline bodies, and fibrosis. NASH is usually asymptomatic, but it can present later as cirrhosis of the liver or hepatocellular carcinoma. The worldwide prevalence of NAFLD is estimated to be around 20 - 30% in the general population. Prevalence of NAFLD in Asia is around 5 - 18%. Studies from India suggest a high prevalence of NAFLD varying from 9% to 32%[4]. The prevalence is even higher in high-risk groups like obesity, type 2 DM, hyperlipidaemia and hypothyroidism. In general

**Assistant Professor, **Resident, ***Senior Professor, ****Senior Professor and Head, Department of Medicine, Pt. B.D. Sharma University of Health Sciences, PGIMS, Rohtak - 124 001, Haryana.*

Corresponding Author: *Dr Deepak Jain, Senior Professor, Department of Medicine, Pt. B.D. Sharma University of Health Sciences, PGIMS, Rohtak - 124 001, Haryana. Tel: 9416147887, E-mail: jaindeepakdr@gmail.com.*

the progression of fibrosis in NAFL is believed to be uncommon, but NASH progresses more commonly to fibrosis.

Recent studies have shown the increased prevalence of NAFLD in CKD. The presence and severity of NAFLD has been related to the incidence and stage of CKD independently of traditional CKD risk factors. Conversely, the presence of CKD increases overall mortality in patients with NAFLD compared with the general population. Further supporting a pathogenic link between NAFLD and CKD, NASH-related cirrhosis carries a higher risk of renal failure than other aetiologies of cirrhosis, is an increasing indication for simultaneous liver-kidney transplantation, and is an independent risk factor for kidney graft loss and CVD.

Research has shown that the underlying pathogenic mechanisms causing steatosis and renal injury are common to both, such as insulin resistance, chronic systemic inflammation and dyslipidaemia. Insulin resistance (IR), which is the underlying mechanism of metabolic syndrome has been linked to cause chronic damage to the kidney by causing glomerulosclerosis, podocyte loss and proteinuria and also to the liver in the form of steatosis and fibrosis. Even though only a minority of NAFLD patients progress to significant fibrosis, such patients may develop liver cirrhosis and hepatocellular carcinoma, which have high morbidity and mortality.

The gold standard for the diagnosis and staging of NAFLD is liver biopsy (LB). It is an invasive procedure, with a risk for major complications. Ultrasonography (USG) is the simple, cheap and noninvasive test for assessing fatty infiltration of liver; however, it cannot detect the fibrosis which is the main determinant of progression of liver disease. Transient elastography (TE) has been recently developed for detection of liver stiffness. TE has several advantages, it is non-ionizing, easy to perform, results are operator independent, not relying on subjective interpretation. Based on several studies, variable LSM cut-off values for each stage of fibrosis have been reported, with readings of ≤ 7 kPa as no fibrosis, LSM 7.0 - 12.9 as F_1-F_2 and LSM $\geq$ 13 kPa as advanced fibrosis respectively in NAFLD. Overestimation of fibrosis can occur in cases of hepatitis, cholestasis, liver congestion, obesity, and mass lesions if present in the liver. Several fibrosis scores like NAFLD fibrosis score, FIB-4 index, APRI score, BARD score have been developed to estimate the severity of fibrosis. These non-invasive fibrosis markers have been shown to be associated with liver fibrosis in NAFLD patients. These scores are calculated with routine blood investigations and are a handy tool for bedside assessment of liver fibrosis. NAFLD fibrosis score (NFS) is the most studied score, with external validation in 13 studies, including more than 3,000 patients. It incorporates age, glycaemia, BMI, platelet count, albumin, and AST/ALT ratio and presents great accuracy for advanced fibrosis. A NFS score of < -1.455 indicates F_0-F_2 fibrosis, while a score of > 0.675 is in favour of advanced fibrosis[5].

In this study we aimed to evaluate the prevalence of Nonalcoholic Fatty Liver Disease in patients of Chronic Kidney Disease and to determine the severity of Liver Fibrosis in different stages of Chronic Kidney Disease. We also compared efficacy of transient elastography with different fibrosis scores (NFS, FIB-4,APRI) in diagnosing liver fibrosis and estimating its severity.

Material and methods

Study population

All patients > 18 years with chronic kidney disease, not on Renal replacement therapy reporting to Department of Medicine and Nephrology clinic were included into the study. CKD was defined according to KDIGO 2012 guidelines as eGFR $\leq$ 60 ml/min/1.73 m^2 body surface area for $\geq$ 3 months, irrespective of the cause and patients were classified into stages defined by KDIGO 2012 guideline according to eGFR, calculated by the MDRD eGFR equation[6]. The patients having serological evidence of Hepatitis C, Hepatitis B, history of significant alcohol intake of more than 20 g alcohol per day in men and more than 10 g per day in women, drug treatment causing hepatic steatosis, (e.g., corticosteroids), gastrointestinal bypass surgery, pregnancy, failure of transient elastography (obesity, ascites) and contra-indications for elastography (jaundice, right heart failure, fluid overload, ALT $\geq$ 5 ULN, AST $\geq$ 3 ULN) were excluded.

Data collection

Patients were subjected to USG of liver for presence of hepatic steatosis, performed by an experienced radiologist. Diagnosis of fatty liver was based on USG findings like liver parenchymal brightness, liver to kidney contrast, bright vessel wall and deep beam attenuation. Those patients with evidence of fatty infiltration underwent transient elastography for determining the severity of liver fibrosis. Total 140 patients of chronic kidney disease coming to Nephrology clinic were screened. Out of which 100 patients of CKD with evidence of hepatic steatosis on ultrasonography were enrolled into the study. Body mass index was calculated as weight in kilograms divided by square of height in metre. A total of 100 healthy controls who were age, sex and BMI matched were also taken. Laboratory investigations included complete haemogram, renal and hepatic function tests, serum electrolytes, lipid profile, thyroid profile, fasting blood sugar, HbA_1C levels, urine complete analysis and 24-hour urinary protein.

Transient elastography was conducted on "Fibroscan 502" device with M probe having 3.5 MHz frequency, by a single operator. For every patient, median of minimum 10 successful readings were taken with interquartile range (IQR) of ≤ 30%. Patients were classified as No fibrosis (LSM ≤ 7 kPa), F_1-F_2 (LSM 7.0 - 12.9 kPa) and advanced fibrosis (LSM ≥ 13.0 kPa)[7]. Fibrosis scores: APRI, NAFLD fibrosis score and FIB-4 index were calculated and specific cut-off values were taken to categorise liver fibrosis into stages (Table I and II).

Table I: Non-invasive fibrosis scores and formulae.

Score	Formula
FIB-4	[Age (years) × AST (IU/l)]/[platelet count (109/l) × √ALT (IU/l)]
NFS	− 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/l) − 0.66 × albumin (g/dl)
APRI	[{AST (IU/l)/AST (ULN[a])} × 100]/platelet count (10^9/l)

Table II: Fibrosis markers and their cut-off values.

	Advanced Fibrosis	Indeterminate	Advanced fibrosis excluded
NAFLD Fibrosis Score	> 0.675	-1.455 – 0.675	< -1.455
FIB-4 Index	> 3.25	1.45 – 3.25	< 1.45
APRI Score	> 1.5		< 0.5

Statistical analysis

Descriptive statistics were computed as median and mean values. For comparison of quantitative data, Mann Whitney U test and Student's t-test were used. Chi square test with or without Yates correction was used for comparison of qualitative data. Statistical analysis was done using SPSS software v.20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA). Level of significance was set at $p < 0.05$.

Results

Patients of CKD were grouped based upon the eGFR values defined by KDIGO 2012 guidelines as stage 3 (n = 24), stage 4 (n = 30) and stage 5 (n = 46) respectively. Baseline characteristics of the study population are shown in Table III.

Association of Chronic Kidney Disease with Non-alcoholic Fatty Liver Disease

Patients of chronic kidney disease who fit the inclusion and exclusion criteria underwent ultrasonography (n = 140). Out of which, 100 patients were found to have evidence of fatty liver, which indicates a prevalence of 71.4%. A population of age, sex and BMI-matched healthy individuals (n = 100) were taken as controls and hepatic steatosis was seen in 32 individuals on ultrasonography. The prevalence of NAFLD in CKD patients was higher compared to the healthy population and was significantly associated (p value < 0.001) independent of age, sex and BMI.

Table III: Baseline characteristics of study population.

	Stage 3 CKD (n = 24)	Stage 4 CKD (n = 30)	Stage 5 CKD (n = 46)	P value
Age (years)	53 (42, 64)	50 (19, 63)	49 (25, 65)	0.143
Sex (M, F), n	13, 11	16, 14	29, 17	0.640
BMI (Kg/m^2)	24.8 (21.4, 27.3)	23.9 (21.2, 27.4)	24.2 (19.8, 31.1)	0.595
Diabetes, n	12	14	23	0.954
Hb (g/dl)	10.600 (8, 13.1)	10.1 (7.5, 12)	7.8 (5.9, 11.08)	< 0.001
eGFR (ml/min/1.73 m^2 BSA)	35 (31, 47)	21 (11, 29)	7.4 (03, 14)	< 0.001
Blood Urea (mg/dL)	53 (38, 126)	73.5 (48, 156)	207 (21, 302)	< 0.001
Creatinine (mg/dL)	1.8 (1.4, 3.2)	2.8 (2, 5.2)	8 (3.9, 12.9)	< 0.001
Uric acid (mg/dL)	4.5 (2.8, 10.9)	5 (3.8, 11.0)	8.8 (4.6, 14.5)	< 0.001
SGOT (U/L)	37 (17, 64)	42 (27, 66)	44 (24, 73)	0.068
SGPT (U/L)	22.5 (15, 60)	28 (12, 54)	27 (2.9, 66)	0.269
ALP (U/L)	72 (52, 90)	69 (52, 90)	70 (50, 90)	0.868
S. Protein (g/dL)	6.9 (6, 8.8)	7 (5, 7.9)	6 (5, 7)	< 0.001
S. Albumin (g/dL)	3.8 (2, 4.8)	3.8 (2.5, 4)	3 (1, 4)	< 0.001
S. Bilirubin (mg/dL)	0.3 (1.0, 0.630)	0. 600 (0.03, 1.0)	0.600 (0.03, 1.0)	0.209
FBS (mg/dL)	112.5 (80, 236)	97.5 (77, 232)	100 (76, 286)	0.491
HbA1c (%)	6.4 (5.4, 9.5)	6.3 (5, 8.6)	6 (5.3, 10.8)	0.580
Serum TSH (mIU/L)	3.7 (2, 4.5)	3 (2, 4.6)	3.06 (2, 4.7)	0.752
S.Triglyceride (mg/dL)	145 (73, 212)	144.5 (81, 184)	136.5 (83, 209)	0.727
S. Cholesterol (mg/dL)	145.5 (101, 234)	144.5 (101, 256)	142.5 (101, 261)	0.747
HDL(mg/dL)	49 (39, 64)	49 (38, 70)	52 (28, 68)	0.609
LDL(mg/dL)	137.5 (96, 185)	140.5 (104, 180)	127 (59, 188)	0.007
VLDL(mg/dL)	28 (22, 43)	29.5 (16, 42)	29 (17, 43)	0.144

Data expressed as median (Q1,Q3)

These patients were further subjected to transient elastography for determining the severity of liver fibrosis by liver stiffness measurement (LSM). In patients of stage 3 CKD (n = 24), 3 patients had advanced fibrosis, 9 patients had fibrosis F_1-F_2 and 12 patients had no fibrosis. In patients of stage 4 CKD (n = 30), 11 patients had advanced fibrosis, 8 patients had fibrosis F_1-F_2 stage and 11 patients had no fibrosis. In stage 5 CKD (n = 46), 33 patients had advanced fibrosis, 8 patients had fibrosis F_1-F_2 and 5 patients had no fibrosis. With increasing stage of CKD, the severity of liver fibrosis increased. Advanced fibrosis was seen in 12.5% of patients in CKD stage 3, 36.6% in CKD stage 4 and 71.7% in CKD stage 5. From this data, it is clear that NAFLD is significantly associated with CKD and the severity of liver fibrosis increases with increasing stages of CKD (p value 0.04).

Table IV: Association of NAFLD with CKD stages as assessed by USG and transient elastography.

	CKD stages			
	Stage 3 (n = 24)	Stage 4 (n = 30)	Stage 5 (n = 46)	P value
USG grade				
1	17	11	0	< 0.0001
2	7	15	20	
3	0	4	26	
Transient Elastography				
No Fibrosis (n = 28)	12	11	5	0.04
F1-F2 (n = 25)	9	8	8	
Advanced fibrosis (n = 47)	3	11	33	

Table V: Comparison of APRI (AST to platelet ratio) score with fibrosis as assessed by transient elastography.

	Transient Elastography			
	ADF (n = 47)	F1-F2 (n = 25)	NOF (n = 28)	P value
APRI				
No Fibrosis (n = 27)	2	21	4	0.317
Advanced fibrosis (n = 1)	1	0	0	

ADF: Advanced fibrosis. NOF: No fibrosis.

Table VI: Comparison of NAFLD fibrosis score (NFS) with transient elastography.

	Transient Elastography			
	ADF (n = 47)	F1-F2 (n = 25)	NOF (n = 28)	P value
NAFLD Fibrosis score				
No fibrosis (n = 29)	5	21	3	0.03
Advanced fibrosis (n = 44)	38	4	2	

ADF: Advanced fibrosis. NOF: No fibrosis.

Table VII: Comparison of FIB-4 index with transient elastography.

	Transient Elastography			
	ADF (n = 47)	F1-F2 (n = 25)	NOF (n = 28)	P value
FIB-4				
No fibrosis (n = 29)	4	9	18	0.04
Advanced fibrosis (n = 45)	28	10	7	

ADF: Advanced fibrosis. NOF: No fibrosis.

Comparison of Non-Invasive Fibrosis Scores with Transient Elastography

Non-invasive fibrosis scores – APRI, NAFLD fibrosis score and FIB-4 index were calculated and their performance in identifying and grading liver fibrosis were assessed using chi-square test.

APRI score could identify 27 patients as having no fibrosis, out of which 13 patients belonged to CKD stage 3 group, 8 patients belonged to CKD stage 4 group and 6 patients belonged to CKD stage 5 group. Advanced fibrosis could be identified in only 1 patient of CKD. In 72 patients, the grade of fibrosis could not be determined by APRI score. Although APRI score had good sensitivity in identifying patients without liver fibrosis, it could not identify and determine the severity of hepatic fibrosis.

On statistical analysis, it was found out that APRI had a poor performance for identifying and grading the severity of liver fibrosis as compared to TE in patients of CKD (p value 0.317).

NAFLD fibrosis scores revealed 29 patients with no fibrosis. Advanced fibrosis was present in 44 patients of CKD. Advanced fibrosis could be correctly identified in 3 out of 3 patients of CKD stage 3, 9 out of 30 patients in CKD stage 4 and 32 out of 46 patients in CKD stage V respectively. Presence of fibrosis could not be determined in 27 patients. NFS had good sensitivity in identifying patients with advanced fibrosis, however, it could not accurately identify patients with F_1-F_2 grades of fibrosis.

NAFLD fibrosis score was able to independently predict the presence and stage of fibrosis in patients of CKD. The severity of fibrosis increased with increasing stages of CKD. Advanced fibrosis was present in 12.5% of patients in CKD stage 3, 30% in CKD stage 4 and 69% in CKD stage 5.

On further statistical analysis comparing NFS with transient elastography, it was found that NFS was able to identify 38 patients of advanced fibrosis out of 47. NFS was as reliable as transient elastography in identifying patients with advanced fibrosis (p value = 0.03). However, lower grades of liver fibrosis could not be accurately identified.

FIB-4 index scores revealed no fibrosis in 29 patients and advanced fibrosis in 45 patients. 5 patients of CKD stage 3 (n = 24), 7 patients in CKD stage 4 (n = 30) and 33 patients of CKD stage 5 (n = 46) had advanced fibrosis. Grade of fibrosis could not be determined in 26 patients.

FIB-4 index was able to identify the stage of fibrosis in patients of CKD. The severity of fibrosis increased with increasing stages of CKD (p value = 0.03).

On comparing FIB-4 index with transient elastography, statistical analysis showed that the performance of FIB-4 index was comparable to transient elastography in detecting liver fibrosis and quantifying the severity of fibrosis in patients of CKD (p value = 0.04).

Discussion

The pathogenic mechanisms underlying NAFLD

development include increased free fatty acids accumulation, inflammatory cytokines and insulin resistance. NAFLD may alter liver-kidney interactions, including altered renin-angiotensin system activation, antioxidant defense, or lipogenesis, which may contribute to CKD. Another potential link consists of shared susceptibility gene variants between NAFLD and CKD. A recent study conducted by Mantovani *et al*, showed that PNPLA3 polymorphism (I148M variant) was associated with susceptibility to NAFLD development and progression[8]. It was also associated with decreasing eGFR levels and an increased prevalence of CKD in patients with type 2 diabetes. Increases in reactive oxygen species, oxidative stress, and inflammatory response are speculated to be the pathogenic factors involved in NAFLD and CKD. Atherogenic dyslipidaemia (increased small, dense LDL cholesterol, low levels of HDL cholesterol, and high TG levels), which is a common feature of NAFLD, is associated with an increased risk of atherosclerotic diseases including renal endothelial dysfunction and renovascular damage. Recent studies have shown that angiotensin II might also be involved in the progression of NASH as it promotes liver fibrosis and also increases vascular endothelial damage by increased oxidative stress and accelerated atherosclerosis[9]. The contribution toward vascular damage from chronic systemic inflammation could lead to the progression of CKD.

Meta-analysis by Musso *et al* concluded that NAFLD was associated with an increased risk of prevalent and incident CKD[5]. In cross-sectional and longitudinal studies, the severity of NAFLD was positively associated with CKD stages. Study by Mikolasevic *et al*, on 62 CKD patients transient elastography was used to assess liver fibrosis which suggested a high prevalence (85.3%) of NAFLD in these patients[10].

Population based study by Wijarnpreecha *et al* was the first to report the association between the non-invasive fibrosis markers (FIB-4, NFS, APRI, and BARD score) with CKD in adults with ultrasonographic proven NAFLD. High/ intermediate scores of NFS and FIB-4 were associated independently with an increased risk of developing CKD[11]. The findings of this study support the previous studies that showed that FIB-4 is the best marker to distinguish NAFLD patients with CKD compared with other non-invasive fibrosis markers[12].

In a Korean study, NAFLD associated decline in eGFR was higher in patients having proteinuria, low eGFR at baseline, smokers, hypertensives and patients having higher NAFLD fibrosis scores[13].

NAFLD is a frequent comorbidity with CKD with a proportion of patients developing significant liver fibrosis and associated morbidity on long-term. The prevalence is believed to be higher because of higher association of metabolic syndrome with CKD. In our study, we found that NAFLD is significantly associated with CKD with high prevalence in this population. Out of 140 patients of CKD, evidence of NAFLD was found in 100 patients with a prevalence of 71.4 %. The majority of these patients belonged to CKD stage 3 and above. After assessing the severity of liver fibrosis by transient elastography (TE), we found that advanced fibrosis is significantly more prevalent in advanced CKD stage 5 compared to CKD stages 3 and 4. Among all non-invasive markers when compared with transient elastography, NAFLD Fibrosis score and FIB-4 index could reliably predict advanced fibrosis in patients with CKD. Moreover, the severity of advanced fibrosis assessed by NAFLD fibrosis score and FIB-4 index increased with increasing stages of CKD.

To our knowledge, this is one of the few studies demonstrating the association of non-alcoholic fatty liver disease and chronic kidney disease in the Indian population. The prevalence of NAFLD in patients of CKD has also not been studied in the Indian population. Although the gold standard test for diagnosis of NAFLD is liver biopsy, it is an invasive procedure for diagnosis. USG is fairly sensitive for diagnosis of NAFLD, however the findings are subjective. Non-invasive methods like transient elastography and NAFLD scores are easy and rapid methods for predicting advanced fibrosis. For non-invasive assessment, transient elastography has become the gold standard in diseases like chronic hepatitis C and B. Recently, many studies have evaluated transient elastography in NAFLD and found it to be reliable marker of advanced fibrosis.

Recent studies have demonstrated that as the severity of CKD increases, the severity of fibrosis also increases. Patients with CKD stage 5 are more likely to have advanced fibrosis than CKD stage 3 patients. In our study, the severity of liver stiffness was measured by transient elastography. Transient elastography is a highly sensitive screening test to exclude advanced fibrosis in NAFLD. Although optimal cut-off values for staging of fibrosis have varied across studies, a cut-off value of 6.5 kPa can exclude advanced fibrosis with a negative predictive value of 0.91 and LSM values < 12.1 kPa can exclude advanced fibrosis with a negative predictive value of 0.99. A LSM value of ≥ 13 kPa is highly suggestive of advanced fibrosis[14].

Simple serum biomarker panels like APRI, NAFLD fibrosis score and FIB-4 index have shown good accuracy in detecting advanced fibrosis in NAFLD patients. We selected these scores for our study because they have been widely validated in NAFLD patients and are relatively easy to perform. In a meta-analysis of 59 studies involving over 12,558 patients of NAFLD, the AUROC values were

found to be 0.77, 0.84 and 0.84 for APRI, NFS and FIB-4 index respectively for detecting advanced fibrosis. The NPV of these scores for excluding advanced fibrosis was high (89 - 93%). However, the PPV values were modest 55 - 67% potentially leading to false positive results. Approximately 30% cases may show indeterminate results[15]. More complicated biomarkers like Enhanced Liver Fibrosis (ELF) score, hepascore are more accurate, but are costly and have less utility in resource limited settings.

In our study, APRI score could detect only one patient with advanced fibrosis and therefore had a poor performance as compared to transient elastography for detection of fibrosis.

FIB-4 score is considered the most accurate score for diagnosing advanced fibrosis in NAFLD. In our study, the performance of FIB-4 Index in detection of advanced fibrosis was comparable to transient elastography. Studies have shown that patients with a higher value of FIB-4 index had greater deterioration of eGFR over a follow-up of 3 years[12].

NAFLD fibrosis score (NFS) is the most studied score, with external validation in 13 studies, including more than 3,000 patients[5,16,17]. In our study, presence of advanced fibrosis could be detected in 44 patients of CKD by NFS. The severity of fibrosis increased with increasing stages of CKD. Performance of NFS was comparable to transient elastography for diagnosing advanced fibrosis in CKD patients.

Limitations of the study

Our study was a cross-sectional study design which does not allow the establishment of a causal relationship between NAFLD and CKD. Second, the diagnosis of NAFLD was not confirmed by liver biopsy. It is known that only liver biopsy can certainly assess the severity of damage and the prognosis. However, liver biopsy would be impractical to perform in routine health examinations. Third, sample size of the study was only 100. Our study population had 49% of diabetes patients. As diabetes patients frequently have higher BMI and more prevalence of fatty liver disease, this could have been a confounding factor in our study.

Conclusion

This study suggests that NAFLD is highly prevalent in CKD patients. The severity of liver fibrosis is negatively associated with the kidney function. Whether interventions to interfere with frequent connection of CKD with obesity, type 2 diabetes, dyslipidaemia would reduce the risk of developing NAFLD is not known. Although current guidelines do not recommend screening for NAFLD in CKD patients, individuals with CKD should be screened for NAFLD even in the absence of classical risk factors. Transient elastography and non-invasive fibrosis markers (NFS and FIB-4 index) are reliable methods for screening advanced fibrosis in CKD patients. However, fibrosis staging could not be determined accurately in up to 30% of patients of NAFLD using fibrosis scores. A concurrent use of fibrosis scores and transient elastography can be used to improve the accuracy. Early diagnosis of NAFLD can help in aggressive management to retard the progression to cirrhosis and decrease the morbidity and mortality associated with chronic kidney disease.

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