

Non-Invasive Assessment of Liver Fibrosis and Steatosis in End-Stage Renal Disease Patients Undergoing Renal Transplant Evaluation

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) has an increased prevalence in end-stage renal disease (ESRD) due to similar risk factors. The aim of this study was to assess non-invasive testing including transient elastography (TE) for liver stiffness (LS), controlled attenuated parameter (CAP) for steatosis, Fibrosis-4 (FIB-4) score, aspartate aminotransferase (AST) to platelet ratio index (APRI) and NAFLD fibrosis score (NFS), for evaluation of NAFLD along with advanced fibrosis (AF) in patients with ESRD undergoing renal transplant evaluation.

Methods: Data were retrospectively collected within 12 weeks of TE. Primary outcomes were AF, defined by LS ≥ 9 kPa compared to APRI > 1.5 , FIB-4 > 2.67 , and NFS of 0.675, and $\geq 5\%$ steatosis by CAP ≥ 263 dB/m compared to liver histology when available.

Results: A total of 171 patients were evaluated: mean age 56, 65% male, 36% obese, 47% had diabetes, 96% hypertension, and 56% dyslipidemia. Mean LS was 6.5 kPa with 21% having AF. Mean CAP was 232 dB/m, with 25% having steatosis. Those with AF were older with higher NFS. Those with steatosis were obese and had diabetes without higher LS or fibrosis scores. Only NFS was associated with LS ≥ 9 kPa. In those with liver histology, AF was associated with LS ≥ 9 kPa but not with APRI, FIB-4, or NFS.

Conclusions: Despite normal liver enzymes, non-invasive assess-

ment via TE in ESRD patients exhibited high prevalence of AF and steatosis not detected by APRI or FIB-4 scores. This high prevalence was secondary to the common risk factors such as obesity and diabetes, among patients with NAFLD and ESRD.

Keywords: Non-invasive fibrosis assessment; Fibrosis-4 score; Fibroscan; Transient elastography; APRI; NFS

Introduction

Among all chronic liver disease etiologies, non-alcoholic fatty liver disease (NAFLD) has the potential to be the leading cause of end-stage liver disease and as such has major transplant implications [1]. Non-alcoholic steatohepatitis (NASH) cirrhosis is the fastest growing etiology of liver failure requiring liver transplant [1-3]. NAFLD has been linked to the development and progression of chronic kidney disease (CKD) and often coexist [4, 5]. This is attributed to the common metabolic syndrome (MS) risk factors for NAFLD and CKD including obesity (body mass index (BMI) ≥ 30 kg/m²), diabetes mellitus (DM), hypertension (HTN) and dyslipidemia (DL) [6-9]. Therefore, hepatic fibrosis may also be highly prevalent in patients with end-stage renal disease (ESRD) on dialysis [10]. Because many with ESRD have normal liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), few undergo liver biopsy [11]. For assessment of hepatic fibrosis, non-invasive testing has mostly replaced liver biopsy. However, the use of these tests among those with concomitant NAFLD and ESRD is unknown.

Liver biopsy is considered to be the gold standard to establish the degree of fibrosis; but due to its invasive nature, it is associated with complications including bleeding, bile leaks, infection, pneumothorax, intestinal perforation and death [12]. The increased bleeding risk in those with ESRD may be due to poor platelet function [11, 13]. Because of these complications and the likelihood of sampling error, there has been interest in non-invasive tests to determine the degree of hepatic fibrosis and steatosis. Transient elastography (TE) and magnetic resonance elastography (MRE) to measure liver stiffness (LS) are two imaging modalities that can be used to detect hepatic fibrosis [14, 15]. Though TE is considered a

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valuable tool in fibrosis assessment, its utility in ESRD patients on dialysis is limited due to chronic volume overload and sampling variability based on probe location [16-20]. Unlike imaging-based TE, serum-based non-invasive tests depend on laboratory parameters including ALT level that tends to be normal in patients with CKD and decrease further with worsening severity of disease [21]. Non-invasive serum-based tests including AST to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores have shown variable diagnostic accuracy for advanced fibrosis dependent on ALT levels in patients with hepatitis C virus (HCV) infection and ESRD [22]. Furthermore, due to normal ALT levels the prevalence of NAFLD in ESRD is unknown and the impact of ALT normalization on non-invasive fibrosis assessment is unclear. To address this gap in knowledge, the aim of this study was to assess the degree of advanced fibrosis and steatosis in patients with ESRD by assessing LS and controlled attenuated parameter (CAP) via TE and to compare performance of TE with other serum-based non-invasive tests.

Materials and Methods

This was a retrospective cohort study designed to describe the presence of hepatic fibrosis and steatosis in patients who had ESRD. All patients were also being evaluated for renal transplant and had non-invasive testing as part of pre-transplant evaluation. Given the poor performance of serum-based tests in those with chronic HCV in those with ESRD [22], both serum- and imaging-based tests were used by our center. Non-invasive tests were identified using a PubMed Search and the selected models were free of additional cost and used routinely available laboratory data. The non-invasive tests included were APRI [23], FIB-4 score [24], and NAFLD fibrosis score (NFS) [25] in addition to TE [26]. The formulas for these models are included here (Supplementary Material 1, www.gastrores.org). These tests were performed on all patients irrespective of underlying etiology for ESRD within 12 weeks of TE. We excluded those individuals with underlying liver disease including hepatitis B, hepatitis C, autoimmune hepatitis, alpha-1-antitrypsin deficiency, Wilson disease, hemochromatosis, primary sclerosing cholangitis, primary biliary cholangitis and those with active alcohol intake to limit any confounders to non-invasive testing interpretation. Clinical data to define metabolic syndrome were collected at the time of TE. Presence of DM, HTN, and DL (increased triglycerides or total cholesterol) were defined by charted clinical diagnosis or use of appropriate treatment medications. Obesity was defined as BMI ≥ 30 kg/m².

The primary outcomes for this analysis were advanced fibrosis (stage ≥ 3) and steatosis ($\geq 5\%$), defined as LS ≥ 9 kPa and CAP ≥ 263 dB/m, respectively on TE [27]. TE was performed after an overnight fast by trained personnel on a non-dialysis day. Unreliability of LS measurement was defined as interquartile range (IQR)/median $> 30\%$, and technical failure was defined by the inability to obtain 10 valid measurements. Only cases with ≥ 10 valid acquisitions were used. Patients on peritoneal dialysis had all peritoneal fluid

drained prior to measurements. TE was performed by experienced providers who performed more than 500 TE prior to the study. Demographic, clinical and laboratory data were collected within 12 weeks of TE. Subsequently, APRI, FIB-4, and NFS were calculated using basic metabolic panel, hepatic panel, complete blood count and international normalized ratio in addition to anthropometric data. Liver biopsy was performed in a subset of population as a required part of the renal transplant evaluation in those suspected of having advanced fibrosis regardless of ALT level or non-invasive test and the results ranged from no fibrosis (F0) to cirrhosis (F4) using Knodell score [28]. The decision to perform liver biopsy was made by the transplant nephrologist, if there was a discrepancy in non-invasive testing suggesting advanced fibrosis that might impact kidney transplant candidacy and not influenced by study inclusion criteria. Slides were stained with Masson's trichrome and evaluated by a hepatopathologist. Advanced fibrosis was defined as either bridging fibrosis (F3) or cirrhosis (F4). The study was approved by the Virginia Commonwealth University Institutional Review Board, and was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

For categorical variables, data were recorded using frequency and percentage. Continuous variables were reported as mean \pm standard deviation (SD) if normally distributed and median with IQR if skewed. Univariate and multivariate analysis were performed to identify factors associated with advanced fibrosis and steatosis. We used analysis of variance (ANOVA) and Student's *t*-test to test for differences in normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Chi-square or Fisher's exact test for categorical variables. Established cutoffs for advanced fibrosis ($\geq F3$) were used for each non-invasive test (APRI > 1.5 , FIB-4 > 2.67 , NFS > 0.675); and for TE, we used LS ≥ 9 kPa and CAP ≥ 263 dB/m [25, 27, 29-31]. In those with available liver histology, the utility of APRI, FIB-4, NFS and LS to predict advanced fibrosis was assessed. All statistics were performed using JMP Pro14 (SAS Institute). All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient cohort

A total of 171 patients were included in our analyses. General characteristics of the cohort are reported in Table 1. The average age was 56 ± 12 years and 65% were male. African Americans were the majority, making 60% of the population. Patients were overweight with BMI of 28.9 ± 5.4 kg/m² with 36% of the population obese with BMI ≥ 30 kg/m². None of the patients had underlying heart failure. XL probe was used in 38% of patients for TE. Metabolic syndrome comorbidities were common with HTN the most prevalent (96%) followed by DM (47%) and DL (56%). The median (IQR) of AST, ALT, and platelet count were 24 IU/L (19 - 35), 18 IU/L (13 - 29),

Table 1. Demographic and Clinical Values of the Study Population

Characteristic	Patient cohort (n = 171)
Age ^a	56 (12)
Male, n (%)	111 (65)
Black, n (%)	102 (60)
Non-Hispanic	99%
BMI ^a (SD)	28.9 (5.4)
BMI ≥ 30, n (%)	61 (36)
Diabetes, n (%)	80 (47)
Hypertension, n (%)	164 (96)
Dyslipidemia, n (%)	95 (56)
AST (IU/L)	31 (29) ^a , 24 (19 - 35) ^b
ALT (IU/L)	29 (45) ^a , 18 (13 - 29) ^b
Platelets (× 10 ³ /mL)	215 (86) ^a , 201 (157 - 262) ^b

^aMean ± SD. ^bMedian (IQR). BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SD: standard deviation.

and 201 × 10³/mL (157 - 262), respectively.

Non-invasive assessment of fibrosis

Table 2 shows detailed assessment of individual non-invasive tests to identify advanced fibrosis (≥ F3) by TE. The median (IQR) of LS assessed by TE was 6.5 kPa (4.7 - 8.9) and 36 (21%) patients had advanced fibrosis (≥ F3). The mean APRI, FIB-4, and NFS were 0.35, 1.97, and -0.408, respectively. APRI, FIB-4 and NFS suggested advanced fibrosis (≥ F3) in three (1.8%), 26 (15%) and 39 (23%) patients, respectively. Table 3 compares those with and without advanced fibrosis

Table 2. Assessment of Each Non-Invasive Test to Identify Advanced Fibrosis and Steatosis

Non-invasive tests	Established cutoffs	Results
Transient elastography (TE)	LS (kPa)	8.3 (7.1) ^a , 6.5 (4.7 - 8.9) ^b
	LS IQR/median ^a	13.2 (5.4)
	LS ≥ 9	21%
	CAP (dB/m) ^a	232 (61)
	CAP IQR ^a	40 (20)
	CAP ≥ 263 (dB/m)	25%
	Probe (M/XL)	62%/38%
AST to platelet ratio index (APRI)	APRI	0.35 (0.39) ^a , 0.025 (0.016 - 0.37) ^b
	APRI > 1.5	1.8%
Fibrosis-4 (FIB-4) score	FIB-4	1.97 (1.33) ^a , 0.72 (1.07 - 2.37) ^b
	FIB-4 > 2.67	15%
Non-alcoholic fatty liver disease fibrosis score (NFS)	NFS	-0.408 (1.61) ^a , -0.385 (-1.56 - 0.51) ^b
	NFS > 0.65	23%

^aMean ± SD. ^bMedian (IQR). LS: liver stiffness; CAP: controlled attenuated parameter; M/XL: medium/large size probe; SD: standard deviation.

Table 3. Comparison of Multiple Variables and Serum-Based Non-Invasive Models With Transient Elastography for Detection of Advanced Fibrosis (LS ≥ 9 kPa)

Variables and models	LS < 9 kPa	LS ≥ 9 kPa	P values
Patients (n)	135	36	
Male (%)	61	75	
Black (%)	59	64	
Age ^a	54 (12)	62 (10)	0.005
%BMI ≥ 30	37	31	
%DM	44	56	
%CAP > 263 dB/m	25	25	
%DL	54	62	
XL probe (%)	38	35	
AST (IU/L) ^a	31.6 (32.7)	30.8 (14.9)	
ALT (IU/L) ^a	29.48 (50.4)	26.2 (19.9)	
Platelets (× 10 ³ /mL) ^a	218 (89)	203 (76)	
APRI ^a	0.35 (0.42)	0.34 (0.23)	
%APRI > 1.5	22	0	
FIB-4 ^a	1.89 (1.27)	2.28 (1.5)	
%FIB-4 > 2.67	20	23	
NFS ^a	-0.560 (1.61)	0.138 (1.52)	0.021
%NFS > 0.675	16	36	0.007

^aMean ± SD. LS: liver stiffness (by transient elastography); BMI: body mass index; DM: diabetes mellitus; CAP: controlled attenuated parameter; DL: dyslipidemia; XL: large probe; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4; NFS: non-alcoholic fatty liver disease fibrosis score; SD: standard deviation.

by TE. Among all non-invasive tests only NFS showed reasonable accuracy to detect advanced fibrosis by TE. The odds ratio (OR) (95% confidence interval (CI)) of having LS ≥ 9

Table 4. Comparison of Multiple Variables and Serum-Based Non-Invasive Models With Transient Elastography for Detection of Steatosis (CAP \geq 263 dB/m)

Variables and models	CAP < 263 dB/m	CAP \geq 263 dB/m	P values
Patients (n)	126	43	
Male (%)	64	65	
Black (%)	57	61	
Age ^a	56 (13)	56 (9)	
BMI (kg/m ²) ^a	27.8 (5.3)	32.2 (4.5)	< 0.0001
%BMI \geq 30	27	64	< 0.0001
%DM	37	74	< 0.0001
%DL	58	54	
%HTN	96	97	
AST (IU/L) ^a	33.8 (33.8)	24 (9)	
ALT (IU/L) ^a	31 (52)	21 (14)	
%APRI > 1.5	2.5	0	
FIB-4 ^a	2.12 (1.43)	1.54 (0.87)	0.017
%FIB-4 > 2.67	18	7	
LS (kPa) ^a	8.7 (7.8)	6.8 (3.9)	
%LS \geq 9 kPa	21	20	
XL probe (%)	27	72	< 0.0001
NFS ^a	0.043 (1.63)	-0.33 (1.59)	
%NFS > 0.675	26	22	

^aMean \pm SD. LS: liver stiffness (by transient elastography); BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; CAP: controlled attenuated parameter; DL: dyslipidemia; XL: large probe; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4; NFS: non-alcoholic fatty liver disease fibrosis score.

kPa if NFS is > 0.65 was 2.94 (95% CI: 1.31 - 6.61). Those with AF were older (62 ± 10 vs. 54 ± 12 years; $P = 0.005$) and had higher NFS (0.138 ± 1.52 vs. -0.560 ± 1.61 ; $P = 0.021$) but there was no relation with sex, race, obesity, DM, steatosis, APRI, or FIB-4.

Non-invasive assessment of steatosis

The mean (SD) CAP was 232 ± 61 dB/m and 43 (25%) patients had steatosis (\geq 5%, Table 2). Table 4 compares those with ($n = 43$) and without ($n = 126$) steatosis by CAP. Those with steatosis had higher BMI (32 ± 4.5 vs. 27.8 ± 5.3 kg/m²; $P < 0.0001$) and obesity (BMI \geq 30 kg/m²; 64% vs. 27%; $P < 0.001$), DM (74% vs. 37%; $P < 0.001$), and increased use of XL probe (72% vs. 27%, $P < 0.001$), but lower APRI (0.24 vs. 0.39; $P = 0.04$) and FIB-4 (1.54 vs. 2.12; $P = 0.017$). There were no differences in NFS or LS by TE between those with and without steatosis by CAP. Multivariate analysis identified both obesity (OR: 3.56, 95% CI: 1.57 - 8.0) and having DM (OR: 4.88, 95% CI: 2.08 - 11.47) as independent predictors of steatosis.

Comparison to liver histology

Table 5 details the clinical, laboratory, non-invasive tests and histologic findings among those that underwent liver biopsy ($n = 14$). The average age of this group was 54 ± 11 years and 64% were male and similar to our overall cohort. Among these subjects, advanced fibrosis was observed in five and correctly classified by TE (as denoted in Table 5) in 10 of the 14 (71%). Conversely, APRI, FIB-4, and NFS correctly classified only 50-57%. Hepatic steatosis was only seen in one and similar to TE for fibrosis was correctly classified by CAP in 71%. None of the patients with advanced fibrosis on biopsy had \geq 5% steatosis indicating an etiology of liver disease other than NASH.

Discussion

The results of our study demonstrate, based on TE, the magnitude of advanced fibrosis and steatosis among patients with ESRD. We show that advanced fibrosis and steatosis assessed by TE and CAP, respectively were 21% and 25%. We also show that steatosis is common and associated with obesity and DM in this population. In those with ESRD, APRI and FIB-4 are not a reliable alternative to TE for these patients. Conversely, NFS did correlate with TE for identifying fibrosis, presumably from NASH given the high proportion with metabolic syndrome. In those with liver histology, TE correctly classified 71% of subjects for both fibrosis and steatosis. This finding is important considering the limited availability of TE for hepatic fibrosis evaluation.

Assessment of advanced fibrosis in ESRD is of utmost importance to gauge the risk of hepatic decompensation after renal transplantation in those with advanced fibrosis. In patients with ESRD and cirrhosis secondary to chronic liver disease, combined kidney-liver transplantation has better outcomes than kidney transplant alone [32]. Despite the increased diagnostic accuracy of non-invasive tests to detect hepatic fibrosis in general population, utility in ESRD is challenging with no studies to date on the subset of possible NAFLD patients undergoing renal transplant evaluation [33]. The major challenge is the reliance of most serum-based non-invasive tests on liver enzymes (AST and ALT) and clinical findings that may be nonspecific because of the underlying renal disease [11, 34]. Rising ALT levels have been directly associated with severity of hepatic fibrosis in patients with chronic HCV with and without ESRD [9, 35, 36]. We have previously demonstrated that diagnostic accuracy of non-invasive test is dependent on ALT levels in ESRD patients with chronic HCV infection [22]. These findings question the utility of non-invasive tests in ESRD that solely rely on laboratory values and anthropometric data for assessment of underlying hepatic fibrosis. In our cohort without HCV, the transaminases were normal likely secondary to underlying renal disease and therefore, APRI and FIB-4 scores were not able to assess advanced fibrosis despite detection by TE in around a quarter of the patients. Thus, we cannot recommend using these serum-based tests in patients with NAFLD and ESRD being evaluated for renal transplant

Table 5. Characteristics Including Clinical, Laboratory, Non-Invasive Tests and Histologic Findings of Subjects Undergoing Liver Biopsy

Age (years)	Gender, M/F	Race, C/AA	BMI (kg/m ²)	DM, Y/N	HTN, Y/N	DL, Y/N	ALT (U/L)	APRI	FIB-4	NFS	TE (kPa)	CAP (dB/m)	AF (F3 - 4)	Steatosis (≥ 5%)
60	F	AA	16.3	N	Y	N	178	2.38	5.35	-1.549 ^a	7.3 ^a	206 ^a	N ^a	N ^a
67	M	AA	27.1	N	Y	N	26	0.31 ^a	2.00 ^a	-0.716 ^a	3.9 ^a	302	N ^a	N
63	M	AA	25.9	N	Y	Y	41	0.42	2.09	-1.026	21.6 ^a	251 ^a	Y ^a	N ^a
39	M	AA	26.1	N	Y	N	14	0.15 ^a	0.76 ^a	-2.219 ^a	5.9 ^a	203	N ^a	N/A
65	F	C	32.3	Y	Y	Y	9	0.140 ^a	1.50 ^a	0.342 ^a	17.1	245 ^a	N	N ^a
45	M	AA	26.4	Y	N	N	9	0.26 ^a	1.92 ^a	1.708	14.4	178 ^a	N	N ^a
63	M	C	28.4	N	Y	N	42	0.52 ^a	2.54 ^a	-0.400 ^a	11.1	262	N	Y
56	M	C	24.4	N	Y	Y	167	2.76	5.98	-0.140 ^a	8.9 ^a	223 ^a	N ^a	N ^a
42	M	C	37.5	Y	Y	N	15	0.16 ^a	0.86 ^a	-0.448 ^a	16.2	340	N	N
66	F	C	21.6	N	Y	N	46	0.32	1.55	-2.236	26.3 ^a	100 ^a	Y ^a	N ^a
54	M	C	23.9	Y	Y	Y					26.3 ^a	173 ^a	Y ^a	N ^a
34	F	AA	29.7	N	Y	N	86	0.55 ^a	1.00 ^a	-1.946 ^a	6.6 ^a	100 ^a	N ^a	N ^a
51	F	C	28.3	N	Y	N	20	0.37	2.11	-0.477	23.9 ^a	334 ^a	Y ^a	N
60	M	AA	40	Y	Y	N	15	0.16	1.24	0.751	21.3 ^a	248 ^a	Y ^a	N ^a

^aRepresenting those with concordant APRI, FIB-4, NFS, or TE with histology for advanced fibrosis (AF) and steatosis. M: male; F: female; C: Caucasian; AA: African American; Y: yes; N: no; DM: diabetes mellitus; HTN: hypertension; DL: dyslipidemia; ALT: alanine aminotransferase; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4; NFS: non-alcoholic fatty liver disease fibrosis score; TE: transient elastography; CAP: controlled attenuated parameter; AF: advanced fibrosis; N/A: not available.

who have normal ALT levels. However, since NFS includes BMI and DM, both associated with NASH, it is not surprising that it outperformed APRI and FIB-4 in this population. Subsequently, given the moderate performance of TE compared to histology in our subset, other non-invasive methods for fibrosis assessment such as MRE need to be studied in this population. Although studies have shown MRE to have higher diagnostic accuracy than TE in fibrosis assessment, the latter has not been validated in ESRD and one has to be cautious about timing of TE in relation to hemodialysis (HD) sessions [18, 37, 38].

TE in renal transplant recipients can detect NAFLD and the degree of fibrosis in those with chronic viral hepatitis but there are limited data on detection of NAFLD in ESRD patients especially those undergoing renal transplant evaluations [39, 40]. Similarly, though TE is superior to APRI in HCV and ESRD, there is paucity of data on accuracy of TE and its comparison with other non-invasive tests in ESRD and NAFLD patients [41, 42]. In this study, we demonstrate the difficulties of applying three common non-invasive serum-based tests, APRI, FIB-4, and NFS to diagnose NAFLD and fibrosis among dialysis-dependent ESRD patients. Among all the non-invasive tools, TE and NFS showed only moderate ability to predict advanced fibrosis and thus the optimal use of these tests is to predict those who lack advanced fibrosis (i.e., negative predictive value). Therefore, these patients with low scores can be spared a liver biopsy. However, if advanced fibrosis is suspected, confirmatory testing such as liver biopsy may still be required. Based on our data, APRI and FIB-4 score are not reliable in assessment of advanced fibrosis in patients

with ESRD and NAFLD undergoing renal transplant evaluation. Though NFS and TE can be combined to increase detection of advanced fibrosis, combining TE with APRI and FIB-4 does not provide similar benefit in these patients.

Our study has several limitations. In addition to the retrospective design, there was concern of selection bias, as recruitment of patients was based on referral practices for renal transplantation at our institution. We used CAP ≥ 263 dB/m as threshold for steatosis; however, lower thresholds including 238 dB/m [43] and 248 dB/m [44] have also been validated for hepatic steatosis evaluation in NAFLD patients. Therefore, our results might vary if different thresholds were used. We selected a CAP threshold of 263 dB/m due to its high sensitivity (90%) for detecting at least 5% steatosis compared to liver histology [27]. Our sample size was moderate (n = 171) which might impact the results. Because length of time on dialysis was not consistently reported, we were not able to assess its impact on fibrosis or steatosis. The impact of statins on steatosis was not assessed because the majority of the cohort had DL, the statins and doses were adjusted over time to control high cholesterol, and there is limited impact of statins on steatosis [45]. This study also occurred at a single institute with majority of population being African American men and as such the results may not be generalizable among different races or a female-predominant population. Though we excluded patients with active alcohol intake, those with remote history of alcohol use were not excluded. Though the overall cohort had non-invasive fibrosis assessment, the number of liver biopsies performed was small (n = 14), and therefore the true accuracy of each test, including TE could not be made. However, because

liver biopsy would not be performed in all those with ESRD, especially those with normal ALT, this question may never be answered. A 12-week window was selected between these tests to reduce clinical status change that would influence non-invasive hepatic fibrosis assessment. We have to acknowledge that most institutes including ours have adopted non-invasive assessment of fibrosis in patients undergoing renal transplant evaluation as liver biopsy is an invasive modality with limitations [16-19]. However, there are only limited data on the diagnostic accuracy of non-invasive tests in ESRD, and it has not been addressed in patients undergoing renal transplant evaluation. Therefore, our results are important and novel as it addresses the utility of non-invasive assessment of hepatic fibrosis in ESRD patients without viral hepatitis undergoing renal transplant evaluation. Fibrosis assessment is important in these patients as in addition to gauging the risk of hepatic decompensation post kidney transplant it also aids in identifying potential patients for combined liver-kidney transplantation. While features of the metabolic syndrome were common in our cohort, the cross-sectional nature of our analysis could not address if ESRD contributed to NAFLD or if NAFLD contributed to ESRD. Although almost one-quarter of our cohort had steatosis, it is unclear if steatosis itself, independent of fibrosis, impacts post-renal transplant survival.

In conclusion, in ESRD patients, our data suggest that advanced fibrosis ($LS \geq 9$ kPa) and steatosis ($CAP \geq 263$ dB/m) by TE were common (21-25%) despite normal liver enzymes. This was not detected by APRI or FIB-4 though fibrosis could be detected by NFS. When compared to liver histology in a smaller group, TE had moderate ability to predict advanced fibrosis in these patients. NFS, but not APRI or FIB-4, was also associated with advanced fibrosis confirmed by liver biopsy. Therefore, we recommend that TE and NFS be used to identify ESRD patients that are at low risk for advanced fibrosis. Since liver biopsy is rarely done in ESRD patients with normal ALT levels and TE and NFS are suboptimal, future studies using MRE for both fibrosis and steatosis assessment with histology as the gold standard are needed to better identify patients with advanced liver disease especially in those undergoing renal transplant evaluation.

Supplementary Material

Suppl 1. Formulas for selected non-invasive tests.

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Conflict of Interest

None to declare.

Informed Consent

Patients were not required to give informed consent to the study because the analysis used anonymous data.

Author Contributions

Syed Taseen: study design, data retrieval, manuscript drafting, revisions and approval of submitted version of the manuscript. Chadha Nikita: data retrieval, manuscript drafting and approval of submitted version of the manuscript. Kumar Dhiren and Gupta Gaurav: critical appraisal and revision of the final manuscript, and approval of submitted version of the manuscript. Sterling Richard K: principal investigator, who conceived, supervised, reviewed, and approved the final manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

ESRD: end-stage renal disease; NAFLD: non-alcoholic fatty liver disease; TE: transient elastography; CAP: controlled attenuated parameter; LS: liver stiffness; NFS: NAFLD fibrosis score; APRI: AST to platelet ratio index; AF: advanced fibrosis; NIT: non-invasive test; DM: diabetes mellitus; HTN: hypertension; DL: dyslipidemia; MRE: magnetic resonance elastography; CKD: chronic kidney disease; SD: standard deviation; IQR: interquartile range; SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; BMI: body mass index; HCV: hepatitis C

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