The Association of Fibrosis-4 (FIB 4) index with Chronic Kidney Disease Among Type 2 Diabetes Mellitus Patients with Concomitant Non-Alcoholic Fatty Liver Disease: A Single Center Cross-sectional Study

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Abstract

Background. Non-alcoholic fatty liver disease (NAFLD) is prevalent in patients with Type 2 Diabetes Mellitus (T2DM) and is associated with chronic kidney disease (CKD). The aim of this cross-sectional study was to determine the association of Fibrosis-4 (FIB-4) index with CKD among T2DM patients with concomitant NAFLD.

Methodology. A single center, analytical cross-sectional study was conducted among 216 T2DM patients with concomitant NAFLD. Clinical data were obtained via retrospective review of medical charts. The outcome of interest was CKD which was based on self-report obtained from medical charts or estimated Glomerular Filtration Rate (eGFR) <60mL/min result nearest to the date of liver ultrasound. FIB-4 index of patient on admission was calculated using an online calculator and subjects were grouped into low, moderate and high risk of developing severe fibrosis depending on their FIB-4 index. In order to determine the association between FIB-4 index and CKD, logistic regression analysis was performed.

Results. Higher FIB-4 index was found to be significantly associated with CKD. Patients with FIB-4 index of 1.45-3.25 (moderate risk) and >3.25 (high risk) have about 3 times higher odds of CKD. However, after controlling for the significant confounders, only those who belong to high-risk group was found to be associated with CKD.

Conclusion. This study has demonstrated that FIB4 index > 3.25, an index of liver fibrosis, is significantly associated with development of CKD in T2DM patients with concomitant NAFLD.

Keywords: Diabetes Mellitus, Non-alcoholic Fatty Liver Disease, Fibrosis-4 Index, FIB-4, chronic kidney disease

Introduction

Diabetic Kidney Disease (DKD), a common complication of diabetes mellitus, is a leading cause of End Stage Renal Disease (ESRD) globally. Early detection and management of earlier stages of DKD slows down the progression toward ESRD.[1-3] Family history of DKD, smoking history, glycemic and blood pressure control, and plasma lipid levels are some of the established factors for identifying people at a greater risk of developing DKD and its progression. Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as an important factor in the development and progression of Chronic Kidney Disease (CKD), both in the non-diabetic and diabetic populations.[6-13] Research indicates that the presence of NAFLD significantly increases the risk of incident CKD, as evidenced by a meta-analysis showing hazard ratio of 1.37 in patients with NAFLD compared to those without.[14] Moreover, diabetes mellitus independently increases the risk of NAFLD, with higher fasting glucose levels correlating with a greater risk.[15] NAFLD can also be diagnosed shortly after the onset of diabetes, further highlighting the intricate relationship between these conditions.[16]

The rise of NAFLD over the recent decades indeed represents a significant shift in the landscape of chronic liver disease globally. Formerly an obscure condition,

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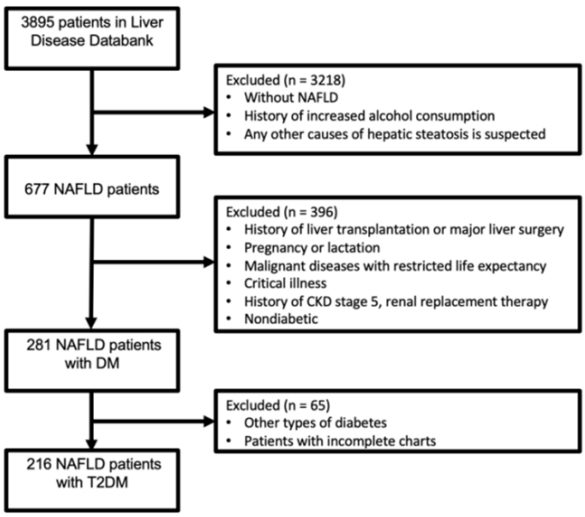

Figure 1. Schematic Diagram of the Study Procedure

NAFLD has now become the leading cause of chronic liver disease worldwide. It encompasses a spectrum of liver conditions ranging from simple steatosis or non-alcoholic fatty liver, to non-alcoholic steatohepatitis (NASH), characterized by inflammation and liver cell damage. Left untreated, NASH can progress to more severe complications, including liver cirrhosis, hepatocellular carcinoma and ultimately death.[17]

The use of non-invasive scoring systems such as the FIB-4 index presents a promising approach for predicting the progression of NAFLD to NASH and liver fibrosis. These scoring systems offer advantages over liver biopsy, including reduced invasiveness, lower risk of sampling errors and cost effectiveness.[18-21] The Fibrosis-4 (FIB-4) index is a high ability non-invasive scoring system used to predict NASH and liver fibrosis.[22–24] It is a simple, inexpensive method that may help identify patients at risk of liver outcomes. In the context of Type 2 diabetes mellitus (T2DM) patients with concomitant NAFLD, understanding the association between FIB-4 index and the risk of developing DKD is particularly relevant. Therefore, we evaluated this in a single-center retrospective cohort study. By elucidating this association, the study could identify a subgroup of diabetic patients who may benefit from more aggressive management strategies to mitigate the risk of CKD development and progression. Ultimately, the findings of this study could inform clinical practice by providing a practical and cost-effective method for risk stratification in T2DM patients with NAFLD, thereby enabling targeted interventions to optimize kidney health outcomes.

Objectives. The general objective of this study is to determine the association between FIB-4 index and CKD among T2DM patients with NAFLD. Specific objectives include 1) to determine the severity of liver fibrosis in diabetic NAFLD patients based on FIB-4 index; and, 2) to determine the prevalence of chronic kidney disease among T2DM patients with NAFLD.

Methodology

Study Design. This is a single center, analytic cross-sectional study conducted at St. Luke's Medical Center, Quezon City, Philippines.

Study Participants. Participants included adult patients diagnosed with T2DM and NAFLD, and were included in the Liver Disease Databank of Liver Disease and Transplant Center in collaboration with Research and Biotechnology group at St. Luke's Medical Center Quezon City. Data were collected via retrospective review of medical charts from January 2007 to July 2021. Criteria for inclusion were: 1) Adult patients ≥18 years old; 2) Diagnosed with T2DM and concomitant NAFLD on admission based on medical charts; 3) Parameters for the calculation of FIB-4 (AST, ALT, Platelet count) available from the medical charts measured ± 2 weeks from the liver ultrasound; and 4) Available estimated Glomerular Filtration Rate (eGFR) result nearest to the date of liver ultrasound.

Criteria for exclusion were: 1) History of liver transplantation or major liver surgery; 2) Pregnancy or lactation; 3) Malignant diseases with restricted life expectancy; 4) Critical Illness; 5) Other types of diabetes; 6) History of increased alcohol consumption (<30g per day for men, <20 g per day for women); 7) History of CKD stage 5, renal replacement therapy; 8) Any other causes of hepatic steatosis is suspected; or 9) Patients with incomplete data or unavailable medical charts.

Operational Definitions

T2DM is defined as personal history of diabetes, history of intake of anti-diabetes medications, or newly diagnosed diabetes (i.e. HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL; two-hour plasma glucose ≥ 200 mg/dL; patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or a random plasma glucose ≥ 200 mg/dL)

NAFLD is defined as ultrasound diagnosed NAFLD in patients who do not have significant alcoholic intake based on history

FIB-4 index of patient on admission calculated using an online calculator (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis). The following parameters were obtained from the medical chart and first laboratory result on admission: age, ALT (U/L), AST (U/L), platelet count ($x10^9$/L).

CKD (chronic kidney disease) was based on patient self-report obtained from medical charts or an eGFR of < 60mL/min/1.73m^2

Study Procedures and Data Gathering. All patients enrolled in the Liver Disease Databank of Liver Disease and Transplant Center in collaboration with Research and Biotechnology group at St. Luke's Medical Center Quezon City from January 2007 to July 2021 who satisfied the inclusion/exclusion criteria were included in the analysis (total enumeration).

Medical history was obtained by reviewing charts of eligible patient using data collection forms (DCF). Items in the DCF included self-reported sociodemographic characteristics, alcohol intake, history of tobacco use, recreational drug use, previously diagnosed liver disease, medical conditions, and use of medications. Clinical assessment included baseline anthropometric measurements and laboratory tests nearest to the date of liver ultrasound (CBC, ALT, AST, HbA1c, FBS, creatinine). The outcome of interest was chronic kidney disease which was based on self-report obtained from medical charts or eGFR < 60 mL/min result nearest to the date of liver ultrasound.

FIB-4 index of patient on admission was calculated using an online calculator (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis). The following parameters were obtained from medical charts and laboratory results nearest to the date of liver ultrasound: Age, ALT (U/L), AST (U/L), platelet count ($x10^9$/L)

Sample Size. PASS15™ software was used to calculate the minimum sample size requirement. Parameters were based from a published study (Ciardulla 2020). Specifying an odds ratio of 6.39, proportion of high FIB-4 equal to 5.4%, and α set at $p < 0.05$, a minimum of 212 patients are required to achieve 80% statistical power.

Statistical Analysis Methods. Data were encoded in MS Excel by the researcher. Stata MP™ version 16 software was used for data processing and analysis. Continuous variables were presented as mean (standard deviation/SD) or median (interquartile range/IQR) depending on the data distribution. Categorical variables were presented as frequencies and percentages. Comparison of continuous variables were performed using One Way ANOVA or *Kruskall Wallis*. Significant ANOVA and *Kruskall Wallis* tests were further analyzed using *Tukey HSD* and *Dunn's Test*, respectively. Categorical variables were compared using *Chi square test* or *Fisher's exact test*.

To determine the association between FIB-4 index and CKD, logistic regression analysis was performed. Screening of potential confounders were performed using simple logistic regression with a $p < 0.20$ criteria. Confounders that will be retained to the model were based on the change-in-estimate criterion of 10%. $P \leq 0.05$ were considered statistically significant.

Ethical Considerations. Participating in this study may not provide direct benefit to the participant. However, information from the study may help in CKD risk prediction and would highlight a subgroup of diabetic patients who should be targeted with more intensive therapy to decrease their risk of developing chronic kidney disease. One of the risks of this study is loss of confidentiality.

Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document was coded and did not contain any identifying information in order to ensure confidentiality.

All study data was recorded and primary investigator was responsible for the integrity of the data i.e., accuracy, completeness, legibility, originality, timeliness, and consistency. Data were stored electronically using a password protected personal laptop which was accessible only to the primary investigator, project leaders and biostatistician. The password was the sole responsibility of the primary investigator.

The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data.

All study-related documents such as all versions of the protocol, ethical clearance, data collection forms and hard copies of source documents were kept and stored in a cabinet with lock and key, located in a secure room only accessible to members of the research team. The key was kept by the project leader. All data material is being kept in strict confidentiality for at least 5 years; after which they will be shredded.

The study abides by the Principles of the Declaration of Helsinki (2013) and was conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP).

The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee.

Results

Of the 3,985 patients enrolled in the Liver Disease Databank of Liver Disease and Transplant Center in collaboration with Research and Biotechnology group at St. Luke's Medical Center Quezon City from January 2007 to July 2021, 216 were included based on the inclusion and exclusion criteria.

Table I shows the demographic and clinical characteristics of the subjects. In general, results showed that the mean age of the respondents was 58.69 with a range of 21 – 91 years old, and most respondents were female (57%). Majority were married and have college level education. Median duration of diabetes mellitus was 5 years. Eighteen (8%) had a T2DM duration of <1 year at the time of study inclusion. Eight percent of patients were not taking any medicine for T2DM and majority (76%) were taking oral medications. Median BMI was 26.54 with a range of 14 – 48. Majority of the subjects were obese. Twenty patients (9%) had preexisting chronic kidney disease and other comorbidities included thyroid dysfunction and cardiovascular disease. Majority were never smokers and non-alcoholic beverage drinkers, and none of the subjects were drug users.

Baseline laboratory parameters are shown in *Table II*.

Table III illustrates the severity of fibrosis among Type 2 Diabetes Mellitus patients with Non-Alcoholic Fatty Liver Disease. Under low-risk group are those whose FIB-4 index are < 1.45. Those who fall under moderate risk are patients who have FIB-4 index of 1.45 – 3.25, and those with > 3.25 are considered high risk for advanced

Table I. Baseline demographic and clinical characteristics (n=216)

Characteristics	N (%)
Age (in years), mean	58.69 ± 13.58
Sex	
Male	93 (43)
Female	123 (57)
Civil status	
Single	30 (15)
Married	147 (76)
Widowed	17 (9)
Highest educational attainment (n=131)	
Elementary	4 (3)
High school	23 (18)
College	104 (79)
DM duration (in years), median	5 (IQR: 3-8.5)
DM medications, % Yes	
None	18 (8)
Oral	164 (76)
Insulin	27 (13)
Oral + insulin	7 (3)
BMI (in kg/m^2)	26.54 (IQR: 23.80-30.07)
Normal	33 (15)
Underweight	8 (4)
Overweight	31 (14)
Obese	144 (67)
Comorbidities	
CKD	20 (9)
Thyroid dysfunction	3 (1)
Cardiovascular disease	10 (5)
Malignancy	0
Smoking status	
Never smoker	170 (79)
Current smoker	12 (6)
Former smoker	34 (16)
Alcohol consumption	
Non-drinker	209 (97)
Former drinker	7 (3)
Drug use	
Non-user	216 (100)
User	0

Table II. Baseline Laboratory Parameters (n=216)

Laboratory Parameters	Median (IQR)
Hemoglobin (in g/dL), median	12.9 (11-14.2)
Hematocrit (in %), median	38.9 (33.8-42.5)
Platelet count (inX10^9/L), median	210 (144.5-285)
ALT (in U/L), median	48.5 (36-69.5)
AST (in U/L), median	37 (25-63)
FBS (in mg/dl), median	129 (107-150.5)
HbA1c (in%), det	6.9 (6.1-7.8)
Lipid profile (n=126)	
Total cholesterol	175.5 (143-209)
Triglycerides	119.5 (86-158)
HDL	45 (37-54)
LDL	107 (81-132)
VLDL	24 (17-31)

Table III. Severity of Fibrosis Among T2DM Patients with NAFLD (n=216)

FIB-4 index	N (%)
<1.45	99 (46)
1.45-3.25	30 (29)
>3.25	55 (25)

fibrosis. The median FIB-4 index was 1.57 [IQR: 0.79-3.36, Range: 0.22-19.32]. Ninety-nine (46%) belong to low-risk category meanwhile, 55 patients (25%) fall on the high-risk category.

Table IV shows the demographic and clinical characteristics by severity of fibrosis. The following variables were significantly different across the three FIB-4 index categories: age, civil status, T2DM duration, Insulin use, hemoglobin, hematocrit, platelet count, AST, FBS, HbA1c, creatinine and eGFR. The mean age of patients under low risk was significantly lower compared to moderate risk ($p < 0.0001$) and high-risk category ($p < 0.0001$). There was no statistically significant difference in mean age seen between moderate vs high risk group ($p=0.070$).

Median T2DM duration significantly differ across groups. Further analysis showed that median T2DM duration of those in the low-risk group was shorter compared to other two groups ($p < 0.00001$). There was no statistically significant difference in median duration between moderate vs. high-risk group ($p = 0.1760$). Insulin use was statistically significantly lower in patients in the low-risk group compared to the two groups ($p = 0.016$). Platelet count showed a decreasing trend for each level of FIB-4 index and were statistically significantly different across all groups by pairwise comparison ($p = 0.05$). AST showed an increasing trend for each level of FIB-4 index, and were significantly different across all groups by pairwise comparison ($p < = 0.05$).

FBS was significantly higher in high-risk group versus low risk ($p = 0.0008$) and moderate risk groups ($p = 0.0421$). No significant difference was seen between low risk and moderate risk groups (p = 0.0991). Compared to low-risk group, creatinine was significantly higher in moderate risk ($p=0.0068$) and high risk ($p=0.0084$) groups. No significant difference between moderate and high-risk groups ($p=0.4942$) was seen. Compared to low-risk group, eGFR was significantly lower in moderate ($p=0.0020$) and high risk ($p<0.00001$) groups. There was no significant difference noted between moderate and high risk ($p=0.1504$) groups.

Compared to low-risk group, total cholesterol of those in the high-risk group was significantly lower ($p=0.0071$). There was no significant difference between low risk and moderate risk ($p=0.0873$), and moderate and high-risk groups ($p=0.1323$). Compared to low-risk group, LDL of those in the high-risk group was significantly lower ($p=0.0029$). No significant difference between low risk and moderate risk ($p=0.0750$), and moderate risk and high-risk groups ($p=0.0924$). There were no significant differences across the three groups in terms of sex, educational attainment, oral T2DM medication, BMI category, comorbidities, smoking status, alcohol consumption, ALT, HbA1c, Triglycerides, HDL, and VLDL.

Table IV. Demographic and Clinical Characteristics by Severity of Fibrosis (n=216)

	FIB-4 INDEX			P value
CHARACTERISTICS	Low risk (n=99) n (%)	Moderate risk (n=30) n (%)	High risk (n=55) n (%)	
Age (in years), mean	52.07 ± 12.89	61.95 ± 11.71	66.91 ± 10.79	<0.00001*[a]
Sex				
Male	40 (40)	31 (50)	22 (40)	0.425[b]
Female	59 (60)	31 (50)	33 (60)	
Civil status				
Single	15 (17)	8 (15)	7 (13)	
Married	71 (81)	39 (75)	37 (69)	0.023*[c]
Widowed	2 (2)	5 (10)	10 (19)	
Highest educational attainment (n=131)				
Elementary	4 (6)	0	0	
High school	12 (17)	6 (20)	5 (17)	0.703[c]
College	55 (77)	24 (80)	25 (83)	
DM duration (in years), median, (IQR)	3 (1-5)	5 (5-10)	7 (5-10)	0.0001*[d]
DM medications, % yes				
Oral	82 (83)	47 (76)	42 (76)	0.461[b]
Insulin	8 (8)	13 (21)	13 (23)	0.016*[b]
BMI (in kg/m^2)				
Normal	14 (14)	9 (15)	10 (18)	
Underweight	3 (3)	3 (5)	2 (4)	0.777[c]
Overweight	11 (11)	10 (16)	10 (18)	
Obese	71 (72)	40 (65)	33 (60)	
Comorbidities, %yes				
CKD	6 (6)	8 (13)	6 (11)	0.307[b]
Thyroid dysfunction	0	2 (3)	1 (2)	0.157[c]
Cardiovascular disease	2 (2)	3 (5)	5 (9)	0.158[c]
Malignancy	0	0	0	-
Smoking status				
Never smoker	77 (78)	50 (81)	43 (78)	
Current smoker	6 (6)	5 (8)	1 (2)	0.464[c]
Former smoker	16 (16)	7 (11)	11 (20)	
Alcohol consumption				
Non-drinker	96 (97)	59 (95)	54 (98)	0.701[c]
Former drinker	3 (3)	3 (5)	1 (2)	
Drug use				
Non-user	99 (100)	62 (100)	55 (100)	-
User	0	0	0	
Hemoglobin (in g/dL), median, (IQR)	13.6 (12.7-14.6)	12.9 (11.1-14.3)	10.8 (9.4-12.8)	0.0001*[d]
Hematocrit (in %), median, (IQR)	40.8 (37.5-43.5)	38.9 (34.7-42.3)	32.7 (28.9-38.2)	0.0001*[d]
Platelet count (inX10^9/L), median, (IQR)	274 (225-339)	182 (146-216)	115 (85-144)	0.0001*[d]
ALT (in U/L), median, (IQR)	49 (35-69)	44 (32-65)	50 (42-77)	0.2604[d]
AST (in U/L), median, (IQR)	28 (20-35)	41 (32-59)	67 (50-99)	0.0001*[d]
FBS (in mg/dl), median, (IQR)	120 (100-145)	131 (108-145)	140 (114-156)	0.0072*[d]
HbA1c (in%), median, (IQR)	6.8 (6.1-7.7)	7 (6.3-8)	6.6 (6.-7.4)	0.0804[d]
Creatinine (in mg/dl), median, (IQR)	0.9 (0.8-1.2)	1.2 (0.9-1.6)	1.1 (0.9-1.6)	0.0135*[d]
eGFR (in ml/min), median, (IQR)	79.2 (54.1-94.5)	57.6 (43.5-84.1)	57.3 (40.1-77.2)	0.0001*[d]
Lipid profile (n=126)				
Total cholesterol (in mg/dl), median, (IQR)	184.5 (159-217)	169 (140-214)	160 (129-182)	0.0405*[b]
Triglycerides (in mg/dl), median, (IQR)	126 (88-166)	131 (86-159)	103 (84-123)	0.2222[b]
HDL (in mg/dl), median, (IQR)	45 (36-54)	46 (40-54)	42 (35-49)	0.4997[b]
LDL (in mg/dl), median, (IQR)	120.5 (93-135)	103 (75-149)	92 (72-112)	0.0183*[b]
VLDL (in mg/dl), median, (IQR)	24.5 (17-33)	26 (17-32)	21 (17-25)	0.2585[b]

[a]One Way ANOVA was used; [b]*Chi square test* was used; [c]*Fisher's exact test* was used; [d]*Kruskal Wallis* test was used; FIB-4 Index: Low risk <1.45; Moderate risk 1.45-3.25; High risk >3.25 Table 5 shows the prevalence of Chronic Kidney Disease among T2DM patients with NAFLD. Median eGFR was 67.50 (46-87.7, range: 4.3-131.1). Of the 216 patients included in the study, 92 patients have CKD (based on eGFR<60) at the time of study inclusion. The prevalence of CKD in this population is 42.59%.

Table VI shows the association between FIB-4 index and CKD. Higher FIB-4 index was found to be significantly associated with CKD. Compared to patients with FIB-4 index of <1.45, patients with FIB-4 index of 1.45-3.25 and >3.25 have about 3 times higher odds of CKD. However, after controlling for the significant confounders, only FIB-4 index > 3.25 was found to be associated with CKD. Patients with FIB-4 index > 3.25 was found to have about two times higher odds of CKD than those with FIB-4 index of < 1.45

Table V. Prevalence of CKD among T2DM with NAFLD

No. of T2DM NAFLD patients with CKD	Total no. of T2DM NAFLD patients	Prevalence (95% CI)
92	216	42.59% (95% CI: 36.13-49.32%)

Table VI. Association between FIB-4 index and CKD among T2DM with NAFLD (n=216)

FIB-4 index	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
<1.45	Ref	Ref	Ref	Ref
1.45-3.25	2.75 (1.42-5.32)	0.003*	2.02 (0.97-4.22)	0.061
>3.25	2.90 (1.46-5.75)	0.002*	2.42 (1.11-5.28)	0.027*

Ref: Reference category; [a]Adjusted for the confounding effects of DM duration and HbA1c

Discussion

In this study we determined the severity of liver fibrosis in diabetic NAFLD patients based on FIB-4 index, determined the prevalence of chronic kidney disease among T2DM patients with NAFLD and investigated the association between FIB-4 index and CKD among T2DM patients with NAFLD. More than half of our subjects had moderate to high risk of fibrosis. In the literature, T2DM is not only associated with NAFLD, but it has also been shown to be an independent risk factor for the development of NASH.[25-26] In patients with T2DM, NAFLD has shown a more aggressive clinical course with necroinflammation and fibrosis. In a study by Rocio Aller et. al. among 160 diabetic patients with NAFLD proven biopsy, a rate of fibrosis over 50%, despite good glycemic control was observed. They also noted that high values of HOMA-IR are the main factor associated to liver fibrosis in T2DM patients. Recently, insulin resistance, but not insulin levels, has been associated with worse histological outcomes.[27]

One possible explanation is that the greater degree of insulin resistance drives uptake of free fatty acids by hepatocytes. This hypothesis is also in agreement with the results of the study by Svegliati-Baroni et al. which showed that post-load insulin resistance is associated with severe hepatic fibrosis in NAFLD patients.[28] In our study, the prevalence of CKD (based on eGFR <60) is 42.59%. To our knowledge, our finding suggests slightly higher prevalence as compared to other studies. Luk et al. in 2015 estimated that 35.93% of T2DM patients have CKD.[29] Globally, the overall prevalence of CKD among T2DM patients varied at 6.0–39.3%. These discrepancies across different settings may be attributed to the variations in diagnostic methods used and ethnicities.[30]

Furthermore, in our study, the subjects included are T2DM patients with concomitant NAFLD which is identified by recent studies to be associated with an increased incidence of CKD. Looking further into the demographics and characteristics of the subjects based on the severity of fibrosis, we noted that the following variables were significantly different across the three FIB-4 index categories: age, civil status, T2DM duration, insulin use, hemoglobin, hematocrit, platelet count, AST, FBS, creatinine and eGFR. The mean age of patients under low risk was significantly lower compared to moderate risk and high-risk category. Though there was no significant difference in mean age between moderate vs high risk group, these findings could still reflect age-related changes to liver structure and function. Notably, old age is a risk factor for NAFLD, CKD, and T2DM. Several studies have shown that eGFR decreases and liver fibrosis increases with aging. AST and platelet count were also significantly different across the three FIB-4 index categories.

Based on FIB-4 index formula [age (year) × AST (IU/L)/(√ALT (IU/L) × platelet count (10^9/L))], the FIB-4 index can increase either by aging and an increase in AST to ALT ratio or by a decrease in platelet count. Insulin use was significantly lower in patients in the low-risk group compared to the two groups. This could be explained by the fact that T2DM duration of those in the low-risk group was shorter compared to other two groups and, the therapeutic approach in Type 2 Diabetes patients depends on the stage and duration of diabetes since in early stages insulin resistance predominates however in those with more advanced stage/longer duration of diabetes insulin resistance persists but deficit in insulin secretion is more evident.

In the study of a non-diabetic, healthy Japanese population, they found that higher FIB-4 index is a risk for a subsequent decrease in insulin secretion.[31] A major finding of this study was the association of high FIB-4 index to CKD among patients with T2DM with concomitant NAFLD. This study demonstrated that FIB-4 index > 3.25 has significant association on the development of CKD particularly on that of eGFR < 60. Those who belong to this group has higher probability of CKD.

In a retrospective study done by Yuya Seko et. al. on Japanese patients with Non-Alcoholic Fatty Liver Disease they concluded that a FIB-4 index ≥ 1.30 was an independent risk factor for development of CKD though some of the population included in the study were not diagnosed with T2DM, they found that having T2DM was associated with deterioration of CKD and incidence of CKD in patients with NAFLD.[31] Furthermore, in another study done still among Japanese type 2 diabetes mellitus patients, Haruka Saito et al. also demonstrated that the FIB-4 index > 1.30, has a prognostic impact on development of CKD, particularly on that of proteinuria, but not in the development of eGFR <60.[32] The lower FIB-4 index value that was observed in their study could be explained by the fact that they utilized not only eGFR but also proteinuria as a gauge for onset of DKD which is an earlier manifestation of the disease.

Our study has several limitations. First is that this is a cross-sectional study, thereby precluding the establishment of causal relations between FIB-4 index and CKD. Second, the diagnosis of NAFLD was based on ultrasound read by one sonographer and exclusion of other causes of fatty liver from chart review, but confirmation by liver biopsy was not done. Lastly, CKD was based on patient self-report obtained from medical charts or an eGFR of <60mL/min/1.73m^2 only and development of proteinuria was not considered which is the hallmark of DKD and an independent risk factor for both renal disease progression and cardiovascular disease.

Conclusion

This study demonstrated that FIB-4 index > 3.25, an index of liver fibrosis, is significantly associated with development of CKD in T2DM patients with concomitant NAFLD. Our results may warrant us usefulness of monitoring FIB-4 index in diabetic patients and/or careful consideration and monitoring of renal function in patients with a high FIB-4 index and in those with increases in the index. To ascertain prognostic impact of FIB-4 index on the development of CKD, we recommend future prospective studies.

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