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Prognostic Markers of Severity of Chronic Kidney Disease in Patients with Metabolic Associated Fatty Liver Disease

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ABSTRACT
Background: One risk factor for the occurrence of an event is nonalcoholic fatty liver disease (NAFLD), and the severity of NAFLD can raise the risk of chronic kidney disease (CKD) even more.
Objective: To assess the relationship between the severity of CKD and metabolic associated fatty liver disease (MAFLD)
Patients and Methods: This cross-sectional study was carried out on 60 patients aged from 18 to 80 years old, of both sexes, diagnosed as MAFLD and CKD. All patients were subjected to serum triglyceride level, total, LDL and HDL cholesterol, FBG, serum creatinine, ALT, AST, GGT, eGFR, albuminuria, serum uric acid and ferritin measurements.
Results: There was a significant negative correlation between eGFR and BMI, FBS, LDL, total cholesterol, serum ferritin, AST, ALT, albuminuria, S. creatinine and S. uric acid. There was no significant difference between eGFR with age, HDL, triglyceride, hemoglobin, total leukocytic count, and GGT. There was a significant difference among the grades for both livers, indicating variations in eGFR levels across the different grades in both organs.
Conclusions: Regardless of conventional risk factors, MAFLD was linked to a greater frequency of CKD, and the incidence of CKD was positively correlated with the severity of MAFLD as determined by non-invasive techniques.
Keywords: Prognosis, Markers, CKD, MAFLD.

INTRODUCTION

The rising prevalence of NAFLD and CKD, which affect up to 15% and almost 30% of the general adult population, respectively, has made them global public health issues [1].

CKD causes kidney function to deteriorate irreversibly over time. Furthermore, ESKD, which necessitates replacement treatment and causes early mortality, is a consequence of CKD development [2].

Notwithstanding the presence of other metabolic disorders, such as obesity, hypertension, T2DM, or metabolic syndrome, it has recently been shown that NAFLD is a risk factor for the occurrence of incidents, and its severity might further raise the risk of CKD [3].

A worldwide panel of specialists from 22 nations recently took the initiative to suggest a new nomenclature and description for nonalcoholic fatty liver disease in adults, namely MAFLD, in order to better comprehend the condition [4].

Hepatic steatosis and the coexistence of overweight/obesity or type 2 diabetes, or in lean/normal weight subjects, the presence of hepatic steatosis and the coexistence of two additional risk factors linked to metabolic dysregulation, are the foundations of the recently proposed diagnostic criteria for MAFLD [3].

MAFLD does not include any liver disease etiologies, such as alcohol, viral infections, or medications, and instead bases its criteria on the level of metabolic dysfunction [5]. Consequently, it has been suggested that MAFLD is a better name to refer to the liver disease that is linked to underlying metabolic abnormalities [6]. In comparison to NAFLD, MAFLD was found to be a more accurate and useful definition for identifying patients with fatty liver who are at high risk of liver disease progression. This was confirmed by recent testing and validation of the definition in the third National Health and Nutrition Examination Surveys (NHANES-III 1988–1994) database. The new diagnostic criteria for MAFLD are therefore distinct from those for NAFLD, although they may eventually take their place [7].

This work's objective was to assess the relationship between the severity of CKD and MAFLD.

PATIENTS AND METHODS

This cross-sectional study was carried out on 60 patients aged from 18 to 80 years old, of both sexes, diagnosed as MAFLD and CKD based on history, clinical assessment, imaging and laboratory data, and were subjected to screening of kidney function tests from January 2023 to January 2024 at the Internal Medicine Department of Tanta University Hospitals, Egypt.

Exclusion criteria: Patients with kidney transplantation, presence of liver cancer, autoimmune disease or other malignancies, and patients with thrombosis, embolism or disseminated intravascular coagulation (DIC).

All patients were subjected to complete history taking, physical examination, laboratory investigations [complete blood count (CBC), serum triglyceride level, total, low density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, fasting blood glucose, serum creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), estimated glomerular filtration rate (eGFR), albuminuria, serum uric acid and ferritin] and

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radiological investigations [Pelvi-abdominal ultrasound].

Blood sampling and processing:

After 8-10 hours of fasting, a 10 ml venous blood sample was obtained in simple vacutainer tubes in accordance with quality control and safety procedures. For CBC, 2 mL was added to EDTA. Serum was isolated from the other vacutainer for normal and specific lab tests by fine centrifugation at 3000 rpm for 15 minutes. Serum samples were delivered to the lab for examination within two hours after being collected.
Serum creatinine, complete lipid profile (cholesterol, triglycerides, HDL, LDL), serum uric acid were tested by full automated Chemistry Analyzer (Konelab Thermoscientific Prime 60, Finland).

CKD stages according to eGFR:

Based on the KDIGO guidelines, CKD patients were classified into 5 categories according to eGFR: Stage 1: eGFR>90 ml/min/1.73m^2, stage 2: eGRF 60-89 ml/min/1.73m^2, stage 3a: eGFR 45-59 ml/min/1.73m^2, stage 3b: eGFR 30-44 ml/min/1.73m^2, stage 4: 15-29 ml/min/1.73m^2 and stage 5: <15 ml/min/1.73m^2.

Urine analysis: Was carried out utilizing a dipstick test that was based on proteinuria and random spot urine measurement.

Diagnosis of MAFLD: Fatty liver by ultrasound and at least one condition of the following: [Overweight (obese): BMI ≥ 23, hypertension: Bl pr ≥ 140/90 mmHg, type two diabetes mellitus (FBG ≥126 mg/dl) and dyslipidemia (High triglyceride, low HDL)].

Ethical approval:

The study was carried out with permission from Tanta University Hospitals' Ethical Committee in Tanta, Egypt. The patients gave their signed, informed permission. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis

SPSS version 26.0 was used for the statistical analysis. One-way ANOVA (F) test with post hoc test (Tukey) was used to compare the three groups' quantitative variables, which were expressed as mean± SD. The qualitative characteristics were shown as frequency and percentage (%). The Pearson moment correlation equation was used to correlate several variables. Statistical significance was defined as a two-tailed P value < 0.05.

RESULTS

The mean age of the participants was 62.12±8.54 years, with a male predominance (53.3%) (Table 1).

Table (1): Demographic distribution and co-morbidities profile of the studied patients

		N=60
Age (years)		62.12±8.54
Sex	**Male**	32(53.3%)
	Female	28(46.7%)
BMI (kg/m^2)		35.52±2.26
Fasting blood glucose (FBG) (mg/dl)		147.82±33.70

Laboratory parameters are explained in Table 2.

Table (2): Laboratory parameters of the studied patients

		N=60
Lipid Profile	**LDL (mmol/L)**	133.03±29.39
	HDL (mmol/L)	40.78±7.72
	TAG (mmol/L)	175.28±45.41
Cholesterol (mmol/)		198.33±37.62
CBC	**Hb (gm/dl)**	11.27±1.89
	TLC (k/uL)	7.72±1.90
	PLT (k/uL)	264.35±65.96
S. Ferritin (mg/dl)		184.42±45.01
Liver Function Tests	**AST (U/L)**	32.016±6.31
	ALT (U/L)	35.82±8.72
	GGT (U/L)	41.87±8.75
Kidney function test	**Albuminuria**	590.53±146.86
	eGFR(ml/min/1.73m^2)	40.20±9.88
	S. creatinine (mg/dl)	2.85±0.70
	S. Uric acid (mg/dl)	5.90±1.42

LDL: low density lipoprotein, HDL: How density lipoprotein, TAG: triacylglycerols, CBC: Complete blood count, Hb: Hemoglobin, TLC: total leukocytic count, PLT: Platelets, AST: aspartate aminotransferase, ALT: alanine transaminase, GGT: gamma-glutamyl transferase, eGFR: estimated glomerular filtration rate.

The abdominal ultrasound revealed the distribution of liver and kidney grades, with 41.7% of liver cases classified as Grade II and 43.3% of kidney cases classified as Grade I (Table 3).

Table 3: Abdominal ultrasound findings according to visual analysis of the studied patients

		N=60
Liver	**Grade I**	18(30.0%)
	Grade II	25(41.7%)
	Grade III	17(28.3%)
Kidney	**Grade I**	10(16.7%%)
	Grade II	26(43.3%)
	Grade III	24(40.0%)

There was a significant negative correlation between eGFR and BMI, FBS, LDL, total cholesterol, S. ferritin, AST, ALT, albuminuria, S. creatinine and S. uric acid. There was no significant between eGFR with age, HDL, TAG, Hb, TLC and GGT **(Table 4).**

Table (4): Correlation between eGFR with demographic data, co-morbidities and laboratory parameters

	eGFR (ml/min)	
	r	P
Age (years)	-0.143	0.275
BMI	-0.825	**<0.001***
FBG	-0.864	**<0.001***
LDL (mmol/L)	-0.770	**<0.001***
HDL (mmol/L)	-0.023	0.859
TAG (mmol/L)	0.109	0.407
CHOLESTEROL (mmol/L)	-0.742	**<0.001***
HB (gm/dl)	0.228	0.061
TLC	-0.171	0.190
PLT	0.099	0.453
S. Ferritin (ng/mL)	-0.667	**<0.001***
AST (U/L)	-0.775	**<0.001***
ALT (U/L)	-0.811	**<0.001***
GGT (U/L)	0.208	0.112
Albuminuria	-0.260	**0.045***
S. creatinine (mg/dl)	-0.808	**<0.001***
S. Uric acid (mg/dl)	-0.495	**<0.001***

*: Significant, r: Pearson Coefficients, * significant p value <0.05, BMI: Body mass index, FBG: fasting blood glucose, LDL: low density lipoprotein, HDL: How density lipoprotein, TAG: triacylglycerols, CBC: Complete blood count, Hb: Hemoglobin, TLC: total leukocytic count, PLT: Platelets, AST: aspartate aminotransferase, ALT: alanine transaminase, GGT: gamma-glutamyl transferase, eGFR: estimated glomerular filtration rate.

There was a significant difference among the grades for both livers, indicating variations in eGFR levels across the different grades in both organs **(Table 5).**

Table (5): Relation between eGFR and abdominal US (liver/ kidney)

	eGFR (ml/min)				
	Grade I	**Grade II**	**Grade III**	**F**	**P**
Liver	49.66± 12.12	40.20± 9.08	30.18± 7.99	13.7 37	**<0.001 ***
Kidney	62.02± 10.66	42.59± 4.67	28.51± 4.43	115. 597	**<0.001 ***

*: Significant, US: Ultrasound, eGFR: estimated glomerular filtration.

DISCUSSION

With an estimated global incidence of between 25% and 30%, one of the most common liver diseases in the world is NAFLD [8]. NAFLD encompasses a variety of liver conditions, such as cirrhosis, hepatic steatosis, and NASH with or without fibrosis [5].

Consistent with our results about laboratory findings, **Flores *et al.*** [9] stated that MAFLD patients showed high lipid profile as total cholesterol, TG, LDL, and VLDL. **Chinnadurai *et al.*** [10] who revealed that CBC parameters of MAFLD patients were indifferent to normal as Hb was 10.9-13.6 g/dl and platelets were 176-294/L for total sample. **Yu *et al.*** [11] who demonstrated that greater probabilities of MAFLD were linked to greater ferritin levels (OR 4.655; 95% CI 2.301, 9.418). **Trasolini *et al.*** [12] who declared that ALT was (13-22) U/L, AST was (19-26) U/L, and GGT was (17-36) U/L in MAFLD patients. **Miyamori *et al.*** [13] who showed that uric acid was 5.5±1.4 mg/dl, eGFR was 85±15 mL/min per 1.73m^2, and proteinuria was in 662 from 14141 MAFLD patients.

Concerning abdominal ultrasound, the distribution of liver and kidney grades, with 41.7% of liver cases classified as Grade II and 43.3% of kidney cases classified as Grade I. These outcomes are in accordance with **Kwon *et al.*** [14] who indicated that by ultrasound of 1776 MAFLD patients showed mild steatosis in 1087 cases, moderate steatosis in 634 cases, and severe steatosis in 55 cases.

Our statics revealed a strong and statistically significant negative correlation between eGFR and BMI and eGFR and FBS, while the correlation with age was weak and not statistically significant. These are supported by **He *et al.*** [15] who stated that BMI and WC were negatively correlated with eGFR (P<0.01). Also, **Sun *et al.*** [16] found matched results as they noticed that eGFR was negatively correlated to FBS.

Regarding correlation analysis of eGFR, there was a strong negative correlation with LDL, a weak and non-significant correlation with HDL, a non-significant correlation with TAG and a strong negative correlation with total cholesterol. These findings are ascertained by **Zeng *et al.*** [17] who noticed that eGFR was negatively correlated with LDL and total cholesterol. Added to that, **Marzuillo *et al.*** [18] were on our side as they concluded that severity of MAFLD patients correlate with high level of LDL, high cholesterol, and low eGFR.

Our statics state that there was a strong negative correlation between eGFR with S. ferritin. **Wang *et al.*** [19] found similar results as they observed that there was a positive correlation between the presence of MAFLD and serum ferritin levels.

There was a strong negative correlation between eGFR and AST as well as ALT. On the other hand, there was no statistically significant correlation between eGFR and GGT. Contrary, **Shen *et al.*** [20] were in disagreement with our results as they demonstrated that eGFR was inversely correlated with GGT in NAFLD.

In the context of eGFR, the results revealed significant negative correlations with albuminuria, S. creatinine, and S. uric acid. Also, significant differences among the grades for both liver and kidney. **Hemmelgarn *et al.*** [21] stated that low eGFR represent impairment of kidney function, which could be detected by high creatinine level, albuminuria, elevated uric acid, and grading of kidney imaging by ultrasound.

LIMITATIONS

Because of the tiny sample size, the results might be negligible. The study was in a single center that may

result in different findings than elsewhere. Hepatic steatosis was diagnosed by ultrasound instead of liver biopsy. Its sensitivity ranged from 60% to 94%. We did not have a control group of non-steatotic patients.

CONCLUSIONS

Regardless of conventional risk factors, MAFLD was linked to a greater frequency of CKD, and the incidence of CKD was positively correlated with the severity of MAFLD as determined by non-invasive techniques. In the context of eGFR, it is negatively correlated with LDL, total cholesterol, ALT, AST, kidney functions test, FBS, and BMI. Global public health is challenged by the very widespread and interrelated disorders of MAFLD and CKD. A number of international experts from various nations created and approved a set of consensus statements based on Delphi that offer recommendations on the mechanisms, management, and treatment of both CKD and MAFLD, as well as the connection between the risk of CKD and the severity of MAFLD. These consensus declarations lay forth a plan for managing and preventing these two prevalent and related illnesses early on.

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