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RESEARCH ARTICLE

Correlation Between Non-Alcoholic Fatty Liver and Chronic Kidney Disease

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Abstract:

Background:

NAFLD is an independent risk factor of CKD. CKD prevalences in NAFLD subjects are two times higher than non-NAFLD. The aim of this study is to know the correlation between NAFLD and CKD.

Methods:

Cross-sectional study was conducted on patients who held Abdominal USG in Wahidin Sudirohusodo & UNHAS hospital from January to December 2017. NAFLD subjects are male and female (18-60 years) who met NAFLD criteria and wanted to participate, non-NAFLD as control subjects. NAFLD is fat accumulation in hepatocyte without a history of alcohol consumption or other etiology of chronic liver disease. CKD definition and classification were based on KDIGO 2012. P value <0.05 was considered to be significant.

Results:

From the study period, we found 134 subjects (67 NAFLD subjects and 67 non-NAFLD subjects). Correlation analysis between NAFLD and eGFR showed that NAFLD subjects had more proportion of eGFR <60 ml/min/1.73m^2 than non-NAFLD subjects (40.3% *vs* 16.4%, p=0.002). NAFLD subjects significantly had more proportion of CKD Grade 3 than non-NAFLD subjects (37.3% *vs* 9%) while non-NAFLD subjects had more proportion of CKD Grade 1 and 2 than NAFLD subjects (56.7% *vs* 38.8% dan 26.9% *vs* 20.9%)(p=0.001). Correlation analysis between NAFLD and proteinuria did not show significant results (p=0.051).

Conclusion:

NAFLD subjects correlated with CKD events compared with non-NAFLD subjects.

Keywords: Non-Alcoholic Fatty Liver Disease, Chronic Kidney Disease, Correlation, Proteinuria, KDIGO, Albuminuria.

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1. INTRODUCTION

Chronic Kidney Disease (CKD) is a condition in which structural or functional damage of kidney for >3 months causes implications to the health [1]. The incidence of CKD has increased in recent years worldwide, including in Indonesia [2]. Kidney Disease Improving Global Outcomes (KDIGO) recommends classification of CKD based on etiology, grade of GFR and albuminuria (Cause, Grading, Albuminuria; CGA) [1].

Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the accumulation of fat (>5%) in liver cells without a history of excessive alcohol consumption or any other causes of chronic liver disease through Abdominal Ultrasonography (USG), abdominal CT-scan or liver biopsy [3]. Non-alcoholic fatty liver disease is the most common etiology of chronic liver disease worldwide, especially in developing countries. The prevalence of NAFLD estimated for 20-30% of the adult population in western countries and increased to 90% in morbidly obese subjects [4]. Non-alcoholic fatty liver disease is a chronic liver disease with various clinical spectrums ranging from simple steatosis (fatty liver), non-alcoholic steatohepatitis (NASH) which is characterized by an increase in fibrosis levels, to the stage of liver cirrhosis [3].

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Subjects with NAFLD showed worse clinical outcomes compared to non-NAFLD subjects in the general population, particularly those with liver fibrosis. Examination of liver fibrosis in NAFLD subjects can provide important information regarding the prognosis of the disease [4].

Studies have shown NAFLD as an independent risk factor and contributes to the development of CKD. The prevalence of CKD in NAFLD subjects is 2x higher (20-55%) compared to non-NAFLD subjects (5-30%), in which damage of renal function was significantly associated with the severity of NASH histological [5]. Sesti *et al.* [6] conducted a cross-sectional study on 570 white subjects in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study in Italy in which they found that high-risk subjects for developing liver fibrosis had 5.1-fold increased risk of developing CKD compared with low-risk patients (OR:5,1; 95% CI= 1,13-23,28; p=0,03), whereas intermediate-risk subjects of developing liver fibrosis have 3 times increased risk of developing CKD compared to low-risk patients (OR: 3,01, 95% CI= 0,87-10,32; p=0,07).

A study by Yilmaz *et al.* [7] in Turkey in 87 subjects diagnosed with NAFLD also found that microalbuminuria was independently associated with histological features of NAFLD (stage of fibrosis). Targher *et al.* [8] conducted a study in Italy on 80 NASH subjects and 80 controls which they reported that the NASH group had significantly lower GFR (75,3±12 *vs* 87,5±6 ml/minute/1,73m^2), frequency of albuminuria (14% *vs* 2.5%) and CKD (25% *vs* 3.7%) which were more frequent compared to control group ($p < 0.001$). The relationship between NAFLD and CKD is still poorly understood and the mechanism that relates NAFLD and renal dysfunction to date is still unknown. The underlying mechanism by which NAFLD may contribute to chronic kidney disease remains unclear. Therefore, the purpose of this present study was to clarify the correlation between NAFLD and CKD and to discuss the evidence linking nonalcoholic fatty liver disease with CKD.

2. METHODS

Cross sectional study was conducted in all patients who Underwent Ultrasonography Examination (USG) using GE Logiq P6 Pro in Wahidin Sudirohusodo Hospital Makassar and Hasanuddin University Hospital starting on January – December 2017. The participants then were divided into NAFLD group and non-NAFLD group as a control. The recruitments of samples were based on inclusion criteria. Subjects in the NAFLD group were male or female (16 – 80 years old) with abdominal ultrasonography showing fatty liver without hepatitis B and C status, without advanced liver cirrhosis and hepatoma, without Diabetes Mellitus, hypertension and neoplasm/ cancer and were willing to comply in the study. Control subjects were study population that did not meet the criteria of the NAFLD group.

In all the subjects, questionnaires were given to obtain information about demographic characteristics, disease history, family history and personal habits, then anthropometric and laboratory examinations. Non-Alcoholic Fatty Liver Disease is defined as fat accumulation in liver cells (fatty liver) without a history of alcohol consumption (< 20 g/ day) or other causes of chronic liver disease through abdominal ultrasonography examination, abdominal CT scan or liver biopsy [3]. Chronic Kidney Disease is established if there is a structural kidney disorder through ultrasonography examination, eGFR < 60 ml/ minute/ 1.73m^2 or albuminuria [1].

CKD is divided into 5 grades mainly grade 1 if GFR is ≥ 90 ml/ minute/ 1.73m^2, grade 2 if GFR is 60-89 ml/ minute/ 1.73m^2, grade 3a if GFR is 45-59 ml/ minute/ 1.73m^2, grade 3b if GFR is 30-44 ml/ minute/ 1.73m^2, grade 4 if GFR is 15-29 ml/ minute/ 1.73m^2, and grade 5 if GFR is < 15 ml/ minute/ 1.73m^2, or undergoing renal replacement therapy. Albuminuria is based on the protein test results from the Cobas C6000 analyzer tool (Roche Diagnostics, Milan, Italy) with the category A1 if the result is negative-trace, A2 if the result is positive 1 and A3 if the result is > positive 1 [1].

Study implementation has received ethical clearance from the Ethical Commission of Biomedical Research on Humanities of Faculty of Medicine of Hasanuddin University Makassar. Our study was performed in accordance with relevant guidelines and regulations of the Ethical Commission of Biomedical Research on Humanities of Faculty of Medicine of Hasanuddin University Makassar. Informed consent was obtained from all participants and/or their legal guardians. A descriptive method and statistical test were used for data analysis. Statistical test results are considered significant if p-value is < 0.05. While risk analysis uses Odds Ratio.

3. RESULTS

During the study period, there were 134 subjects consisting of 67 NAFLD subjects and 67 non-NAFLD subjects. The characteristics of subjects are described in Table **1**.

Tabel 1. Characteristics of subjects.

Variabel	n	Minimum	Maximum	Mean	SD
Age	134	19	86	48.3	13.2
eGFR	134	5.2	150.0	83.7	31.2

eGFR: estimated Glomerular Filtration Rate, SD: Standard Deviation

To determine the correlation between NAFLD and CKD in this study, we performed a correlation analysis of NAFLD with eGFR, CKD grade, and the incidence of proteinuria. If eGFR grouped into < 60 and ≥ 60, the proportion of eGFR < 60 was significantly higher in NAFLD subjects than in non-NAFLD (40.3% *vs* 16.4%, p = 0.002) (Table **2**).

Table 2. Correlation between NAFLD with eGFR.

Subject		eGFR		Total	p*
		<60	≥60		
NAFLD	n	27	40	67	0.002
	%	40.3%	59.7%	100.0%	
Non-NAFLD	n	11	56	67	
	%	16.4%	83.6%	100.0%	
Total	n	38	96	134	
	%	28.4%	71.6%	100.0%	

*Chi Square test. eGFR: estimated Glomerular Filtration Rate, NAFLD: non-alcoholic fatty liver disease.

Correlation analysis between NAFLD and grade of CKD was found to be significantly more proportional to grade 3

CKD in NAFLD subjects compared to non-NAFLD (37.3% *vs* 9%). On the other hand, the proportions of grade 1 and 2 CKD were higher in non-NAFLD subjects than NAFLD (56.7% *vs* 38.8% and 26.9% *vs* 20.9%, p = 0.001) (Table **3**).

Correlation analysis of NAFLD with proteinuria showed that A3 proteinuria was more common in NAFLD subjects compared to non-NAFLD, but there was no statistical significance (p = 0.051) (Table **4**).

4. DISCUSSION

In recent studies, it has been shown that NAFLD plays a role in the development of CKD. In CKD patients themselves, they also have a risk of experiencing NAFLD. Some researchers have conducted studies that assess the prevalence of kidney disease in NAFLD subjects [9]. In this study to determine the correlation between NAFLD and CKD, correlation analysis of NAFLD and eGFR, CKD grade, and incidence of proteinuria was performed.

In our study, correlation analysis between NAFLD and eGFR showed a significantly greater proportion of eGFR < 60 in NAFLD subjects compared to non-NAFLD (40.3% *vs* 16.4%, p = 0.002) (Table **2**). Another study by Targher *et al.* [10] in Italy which conducted a study on 2,103 subjects with type 2 DM found that subjects with NAFLD had more CKD compared to non-NAFLD group (15% *vs* 9%). Based on logistic regression analysis, it was found that NAFLD was associated with an increased risk of CKD events (OR 1.87; 95% CI: 1.3-4.1, p = 0.020). Ahn *et al.* [11] conducted a cross-sectional study in Konkuk Korea on 1,706 subjects over 50 years of age in which they found 545 (31.9%) subjects diagnosed as NAFLD. NAFLD group comprised 424 (29.9%) subjects with CKD. Univariate logistic regression analysis found that NAFLD was significantly associated with CKD (OR = 1.69; 95% CI: 1.34 to 2.12) in subjects aged > 50 years.

In this study, correlation analysis between NAFLD and grade of CKD showed significantly more proportions of grade 3 CKD in NAFLD subjects compared to non-NAFLD (37.3% *vs* 9%). On the other hand, the proportions of grade 1 and 2 CKD were higher in non-NAFLD subjects than NAFLD (56.7% *vs* 38.8% and 26.9% *vs* 20.9%, p = 0.001) (Table **3**). Jang *et al.* [12] in his study in Seoul found that more decrease of eGFR were found in NAFLD subjects compared to non-NAFLD after they were being followed up for 6.5 years (-0.79% per year, 95% CI: -1.31%, -0.27% *vs* 0.30%, 95% CI: -0.14%, 0.76%; p = 0.002). Arase *et al.* [13] who conducted a retrospective study of 5,561 subjects with NAFLD in Japan found that progression to CKD in subjects with NAFLD occurred when subjects had eGFR values of 60-75 ml/ minute (HR 2.75; 95% CI= 1.93-3.94; p < 0.001).

Correlation analysis of NAFLD with proteinuria showed that A3 proteinuria was more common in NAFLD subjects compared to non-NAFLD, but there was no statistical significance (p = 0.051) (Table **4**).Yilmaz *et al.* [7] in Turkey conducted a study on 87 subjects diagnosed with NAFLD through a liver biopsy examination and found that microalbuminuria was independently associated with histological features of NAFLD (stage of fibrosis). Targher *et al.* [8] who conducted a study in Italy on 80 NASH subjects and 80 controls showed that the NASH group had significantly lower GFR (75.3 ± 12 *vs* 87.5 ± 6 ml/ minute/ 1.73 m^2, p < 0.001), frequency of albuminuria (14% *vs* 2.5%) and CKD (25% *vs* 3.7%) which were more frequent than the control group (OR: 6.14, 95% CI 1.6-12.8). The insignificant statistical test results in our study are likely due to the examination of proteinuria using the semiquantitative method.

Table 3. Correlation of NAFLD with Grade of CKD.

Subject		Grade CKD				Total	p*
		Grade 4/5	Grade 3	Grade 2	Grade 1		
NAFLD	n	2	25	14	26	67	0.001
	%	3.0%	37.3%	20.9%	38.8%	100.0%	
Non-NAFLD	n	5	6	18	38	67	
	%	7.5%	9.0%	26.9%	56.7%	100.0%	
Total	n	7	31	32	64	134	–
	%	5.2%	23.1%	23.9%	47.8%	100.0%	–

*Chi Square test. NAFLD: non-alcoholic fatty liver disease, CKD: chronic kidney disease

Table 4. Correlation of NAFLD with Proteinuria.

Group		Proteinuria			Total	p*
		A3	A2	A1		
NAFLD	n	9	7	51	67	0.051
	%	13.4%	10.4%	76.1%	100.0%	
Non NAFLD	n	3	15	49	67	
	%	4.5%	22.4%	73.1%	100.0%	
Total	n	12	22	100	134	–
	%	9.0%	16.4%	74.6%	100.0%	–

*Chi Square test. A: Albuminuria, NAFLD: non-alcoholic fatty liver disease.

CONCLUSION

The mechanism that links NAFLD with renal dysfunction to date is still unknown, but in some studies, it is explained that both have the same cardio metabolic risk factors and/ or both have the same pathogenesis mechanism [14]. NAFLD subjects were associated with the incidence of CKD compared to non-NAFLD subjects.

AUTHORS CONTRIBUTION

Hasyim Kasim and St. Rabiul Zatalia wrote the manuscript, Haerani Rasyid and Syakib Bakri revised the manuscript; St. Rabiul Zatalia, M. Luthfi Parewangi, Fardah Akil and Arifin Seweng contributed to the data collection, statistical analysis, and result interpretation. Hasyim Kasim, St. Rabiul Zatalia, Haerani Rasyid and Syakib Bakri proposed the idea, concept, and study design. All authors participated in manuscript discussion and revision. All authors approved the final manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study has received ethical clearance from the Ethical Commission of Biomedical Research on Humanities of Faculty of Medicine of Hasanuddin University, Makassar, Indonesia with reference number 428/H4.8.4.5.31/PP36-KOMETIK /2017.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Informed consent was obtained from all the participants.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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