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WORD COUNT 2512
TIME SUBMITTED 30-APR-2024 04:48PM
PAPER ID 108645952

Word Count – Words: 2,512

ORIGINAL ARTICLE

Risk factor analysis for cognitive impairment in Non-Alcoholic Fatty Liver Disease (NAFLD)

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Abstract

Background and aim: Hepatic lipid accumulation is a defining feature of liver diseases, referred to as non-alcoholic fatty liver disease (NAFLD). There may be a connection between NAFLD and cognitive impairment, namely concerning memory and attention, according to recent studies. This study aimed to define the forms of cognitive deficits associated with these risk variables and determine the factors contributing to cognitive impairment in NAFLD patients. Material and Methods: An analytical observational study was conducted at Wahidin Sudirohusodo Teaching Hospital in Indonesia from 2023 to 2024. A total of 126 NAFLD patients were included, and cognitive function was assessed using the Montreal Cognitive Assessment Indonesia (MoCA-INA) instrument. Statistical analysis was performed using SPSS version 25.

Results: Among the 126 NAFLD patients analyzed, 63 (50%) exhibited cognitive impairment, primarily as memory deficits. Obesity and dyslipidemia were significantly associated with cognitive impairment, with obesity presenting a 4.5-fold increased risk and dyslipidemia a 2.5-fold increased risk. However hypertension and diabetes mellitus did not show significant associations with cognitive impairment.

Conclusions: This study underscores the prevalence of cognitive impairment in NAFLD patients and highlights obesity and dyslipidemia as significant risk factors for cognitive decline in this population. Further longitudinal studies are needed to explore the relationship between NAFLD and cognitive impairment.

Keywords: NAFLD, cognitive impairment, risk factors, MoCA-INA, liver disease, memory

INTRODUCTION

A group of disorders known as non-alcoholic fatty liver disease (NAFLD) include non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver (NAFL). These disorders are all characterized by hepatic lipid buildup. Hepatocellular carcinoma, cirrhosis, and fibrosis may develop from these.[1] The prevalence of NAFLD in the general population in Western countries is 20–30%, while in obese people it is 80–90%.[2] In Asia, the prevalence is approximately 25%, affecting 8 – 19% of individuals with a body mass index (BMI) of less than 25kg/m^2.[3] In Indonesia, comprehensive studies on NAFLD are lacking; however, localized research in Palembang found a prevalence of 7.9%, with 39% of patients having a normal BMI.[4] Ultrasound-diagnosed NAFLD prevalence in Indonesia is reported at 51.04%.[5]

Recent years have seen an association between cognitive dysfunction and NAFLD. Reports indicate that 70% of NAFLD cases result in cognitive function issues, particularly affecting memory, attention, concentration, and causing confusion, which negatively impacts daily life and quality of life.[6] Seo et al.'s study of 4,472 adults aged 20 – 59 found NAFLD independently associated with lower cognitive performance, irrespective of cardiovascular disease and other risk factors, notably affecting memory function significantly.[7]

Prior research has linked NAFLD with poorer cognitive function. Generally, risk factors associated with cognitive impairment include age, education level, history of hypertension, medication use, and high LDL cholesterol levels.[8] Charlotte et al., studying the prevalence and risk factors of cognitive impairment in obesity and NAFLD with 180 subjects, concluded that multidomain cognitive impairment was present in 40% of severely obese individuals, with executive function and memory most affected. Although cognitive impairment is not limited to patients with NAFLD or NASH, being male and having low LDL cholesterol levels are associated with increased risk.[9]

Liu et al., in a longitudinal study of 1,651 participants, of which 795 (48.2%) had NAFLD, investigating NAFLD and cognitive changes in middle-aged and elderly adults, found gender, age, obesity (BMI), hypertension, diabetes mellitus, and dyslipidemia significantly related to cognitive impairment.[10]

Thus, this research aims to investigate the risk factors associated with cognitive impairment in NAFLD patients and identify the types of cognitive impairment based on these risk factors.

PATIENTS AND METHODS

This research utilized an analytical observational approach employing a cross-sectional study design. The study was conducted at Wahidin Sudirohusodo Teaching Hospital in Makassar, South Sulawesi, Indonesia, from 2023 to 2024. The population under study comprised all patients diagnosed with NAFLD at the hospital, with the sample including subjects meeting specific inclusion criteria.

Inclusion criteria encompassed NAFLD patients aged 18 and above who consented to participate, while exclusion criteria comprised individuals with a history of stroke, central nervous system infections, severe head injury, brain tumors, or psychiatric disorders. Based on calculations, a minimum sample size of 63 NAFLD patients was determined. Sampling was conducted using a consecutive sampling method until the sample size was achieved. Data analysis was performed using SPSS version 25, employing descriptive methods and statistical tests such as Chi-square tests for statistical significance ($P < 0.05$).

Operational definitions and objective criteria were established for cognitive function, NAFLD diagnosis, gender, age, diabetes, dyslipidemia, obesity, and hypertension. Cognitive function refers to mental abilities such as attention, learning, memory, problem-solving, and emotional recognition. This is assessed using the Montreal Cognitive Assessment Indonesia (MoCA-INA) instrument, which evaluates the domains of visuospatial, naming, memory, attention, language, abstraction, and orientation, with a total score of ≥ 26, indicating normal functioning, and < 26, indicating impairment. The instrument is conducted with an interview by a clinician for approximately 15 minutes. Following the instructions, patients with less than 12 years of education were scored by adding one point to their overall score. NAFLD diagnosis relies on ultrasound evidence of hepatic steatosis without significant alcohol consumption. Gender is determined biologically, while age is calculated chronologically. The American Diabetes Association 2023 guidelines, which are based on HbA1c ≥ 6.5%, fasting blood glucose ≥ 126 mg/dl, 2-hour plasma glucose following 75-g OGTT ≥ 200 mg/dl, or random blood glucose > 200 mg/dl, were used to diagnose diabetes. The criteria for dyslipidemia include total cholesterol > 200 mg/dl, LDL > 130 mg/dl, HDL > 60 mg/dl, and triglycerides > 200 mg/dl. Obesity is defined by a BMI above 2 standard deviations for age and sex. The diagnosis of hypertension is made by performing a blood pressure measurement examination conducted by a clinician in a quiet place with the cuff level with the heart and a comfortable sitting position. If the systolic pressure ≥ 140 mmHg and diastolic pressure > 90 mmHg are obtained, the criteria for hypertension can be established.

Ethical clearance was obtained from the Biomedical Research Ethics Commission at the Faculty of Medicine, Universitas Hasanuddin (No. 13/UN4.6,4.5.3L I PP36/ ZA24), and informed consent was obtained from participants. The research followed a predefined sequence of activities (Figure 1).

RESULTS

Characteristics of the Patients

In this study, 126 NAFLD patients were analyzed. Females comprised a majority, with 76 subjects (60.3%), compared to 50 males (39.7%). The highest age group was 50-59 years (31%). Obesity was prevalent in 89 patients (70.6%), hypertension in 17 (17.5%), diabetes mellitus in 44 (34.9%), and dyslipidemia in 57 (45.2%) subjects. Cognitive impairment was observed in 63 patients (50%). The most affected cognitive domain was "memory" (82.5%), while the least affected was "naming" (25.4%). Detailed patient characteristics are provided in Tables 1 and 2.

Table 1. Baseline Characteristics of the Patients

Variable	n	%
Gender		
Male	50	39.7
Female	76	60.3
Age		
< 40 years	33	26.2
40 – 49 years	31	24.6
50 – 59 years	39	31.0
≥ 60 years	23	18.3
Obese		
Yes	89	70.6
No	37	29.4
Hypertension		
Yes	22	17.5
No	104	82.5
DM		
Yes	44	34.9
No	82	65.1

Dyslipidemia		
Yes	57	45.2
No	69	54.8
Cognitive impairment		
Yes	63	50.0
No	63	50.0

Table 2. Distribution of Cognitive Impairment Domain

Cognitive Impairment Domain	Patients with cognitive impairment (n=63)	
	n	%
Memory	52	82.5
Executive	49	77.8
Attention	43	68.3
Abstraction	40	63.5
Language	32	50.8
Orientation	20	31.7
Naming	16	25.4

Distribution of Cognitive Impairment by Risk Factors

The distribution of cognitive impairment in this study is illustrated in Table 3 based on risk factors in NAFLD patients. After examining the distribution of cognitive impairment types by risk factor, impairment in the "memory" domain was the most common.

Table 3. Distribution of Cognitive Impairment by Risk Factors

Cognitive impairment domain	Risk factors							
	Obesity		Hypertension		Diabetes mellitus		Dyslipidemia	
	n	%	n	%	n	%	n	%
Executive	42	77.8	6	66.7	13	72.2	28	77.8
Naming	14	25.9	2	22.2	6	33.3	11	30.6
Attention	35	64.8	5	55.6	12	66.7	23	63.9

Language	28	51.9	4	44.4	14	77.8	16	44.4
Abstraction	34	63.0	6	66.7	16	88.9	21	58.3
Memory	47	87.0	7	77.8	13	72.2	31	86.1
Orientation	17	31.5	1	11.1	5	27.8	12	33.3

The Association of Risk Factors and Cognitive Function Impairment in NAFLD

The analysis of the relationship between risk factors and cognitive impairment in NAFLD patients is illustrated in Table 4. Obesity was significantly associated with cognitive impairment, found in 54 subjects ($P < 0.01$). A cross-sectional study by Cook et al., of 299 young female patients aged 18-35 years who were obese confirmed that the obese group had normal performance but was significantly lower in attention and more impulsive than the normal weight group. This may indicate early cognitive decline in obese patients.[11] Other research that supports these findings was also shown by Cserjesi et al., who reported a decrease in attention in middle-aged women with an average age of 48 years with obesity compared to non-obese controls.[12] A longitudinal study conducted by Gunstad et al., reported the same thing where obesity was significantly associated with obesity in 1,703 research subjects; more firmly, they reported that the cognitive disorders found were memory and executive disorders.[13] Hypertension was observed in 9 subjects with cognitive impairment ($P = 0.348$), while diabetes mellitus was found in 18 subjects ($P = 0.135$), and dyslipidemia in 36 subjects ($P < 0.01$) with cognitive impairment. Research conducted by Feinkohl et al., reported that lower HDL cholesterol was significantly associated with a higher likelihood of cognitive impairment.[14] In theory, HDL cholesterol is involved in the deposition and clearance of beta-amyloid which is a factor that plays an important role in inflammation of the endothelium and degeneration. Nerves in the brain.[15] Research by Ma et al., on the relationship between blood cholesterol and cognitive decline in 1,159 patients in China found that higher baseline total cholesterol and LDL cholesterol concentrations were significantly associated with greater cognitive decline.[16]

Table 4. Association between Risk Factors and Cognitive Impairment

Variable	Cognitive impairment (n = 63)		*P-value*
	Yes	No	
Obesity			0.000*
Yes	54	35	
No	9	28	
Hypertension			0.348
Yes	9	13	
No	54	50	
Diabetes mellitus			0.135
Yes	18	26	
No	45	37	
Dyslipidemia			0.007*
Yes	36	21	
No	27	42	

* Chi-Square test ($P < 0.01$)

Multivariate analysis was conducted to determine independent predictors of cognitive impairment in NAFLD patients. The results showed that obesity (OR = 4.5; 95% CI = 1.87 to 10.90; $P = 0.001$) was a more dominant risk factor compared to dyslipidemia (OR = 2.5; 95% CI = 1.15 to 5.27; $P = 0.020$) for cognitive impairment in NAFLD patients. NAFLD subjects who were obese had a 4.5 times higher risk of cognitive impairment compared to non-obese subjects, and those with dyslipidemia had a 2.5 times higher risk compared to those without dyslipidemia, as indicated by the odds ratios.

CONCLUSIONS

In summary, this study investigated cognitive impairment in patients with NAFLD, comprising 126 subjects, among whom 63 (50%) were found to have cognitive impairment. Memory impairment was the most prevalent and consistently observed across all studied risk factors. Furthermore, a significant association was noted between obesity and dyslipidemia with cognitive impairment in NAFLD patients. Specifically, obesity was associated with a 4.5-fold increased risk, while dyslipidemia was associated with a 2.5-fold increased risk of cognitive impairment in NAFLD patients. These findings underscore the importance of addressing obesity and dyslipidemia as potential risk factors for cognitive

impairment in NAFLD. Further longitudinal studies are needed to explore the relationship between NAFLD and cognitive impairment.

Acknowledgements: This study received support from the Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, located in Makassar, South Sulawesi, Indonesia.

Funding: This research received no dedicated funding from governmental, commercial, or non-profit organizations.

Conflict of Interest: All authors declare no conflicts of interest to disclose.

Author's Contribution: RTHB, WU, and NAD are principal investigators. SB and HR contributed to the conceptualization and design of the research. AS contributed to the data's conceptualization, design, and statistical analysis. All authors were involved in drafting the manuscript, revising it, and evaluating its content. They have all read and approved the manuscript, confirming the accuracy and integrity of the research details.

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