

Correlation between Steatosis Degree and Hypertension Degree in Non-Alcoholic Fatty Liver Disease Patients in Indonesia

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Abstracts: Non-alcoholic fatty liver disease (NAFLD) has been recognized closely linked to cardiovascular diseases including hypertension. The connection between these conditions can be attributed to lipotoxicity, that induces systemic inflammation by activating the sympathetic nervous system (SNS) and triggers the release of angiotensin II within the renin-angiotensin-aldosterone system (RAAS). This study examined the correlation between degree of steatosis and degree of hypertension in NAFLD patients at Hajj Hospital Jakarta in 2019-2022. A cross-sectional approach was used to analyse the medical record data obtained through consecutive sampling. B-mode abdominal ultrasound examination assessed the degree of steatosis in NAFLD. Blood pressure grading was based on the 2020 International Society of Hypertension (ISH) Global Hypertension Practice Guidelines. The data were processed using Somers'd test to define the correlation between steatosis and hypertension. Of 53 NAFLD subjects, 56.6% were female, and mild steatosis was dominant (54.7%). The proportion of hypertension among NAFLD patients was 39.7%, with a higher prevalence of 61.9% among those aged 50 years or older. Majority of patients were grade I hypertension, whereas all subjects with grade II hypertension exhibited severe steatosis. There was correlation between the degree of hypertension and steatosis patients with NAFLD, with a p-value of 0.029 and a weak correlation coefficient ($r= 0.251$). This study found a correlation between steatosis and degree of hypertension. It was suggested females aged 50 years or older with grade II hypertension should be screened for fatty liver.

Keywords: Non-Alcoholic Fatty Liver Disease, Hypertension, Steatosis Degree, Hypertension Degree, Correlation.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a medical condition indicated by the accumulation of lipids in hepatocytes, exceeding 5% of the liver weight, in individuals who do not consume alcohol surpassing 60 g/day for males and 40 g/day for females [1,2]. This disease has various causes, including dyslipidaemia, obesity, insulin resistance or diabetes mellitus, medication use, toxicity, and idiopathic factors.³ NAFLD contains a spectrum of diseases, varying from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) [1]. Diagnostic methods for NAFLD include imaging methods such as ultrasonography, liver elastography, and magnetic resonance elastography (MRE), as well as histological examination to determine the presence of steatosis and steatohepatitis, as well as staging and grading [2,3].

NAFLD refers to a condition indicated by two primary criteria: (a) liver steatosis, which can be observed through imaging techniques or histological examination; and (b) the absence of any secondary factors contributing to liver steatosis, such as excessive alcohol consumption, medication use, Wilson's disease, or conditions associated with micro-vesicular steatosis [3].

The "multiple-hit" theory is widely recognized as the pathogenic model for NAFLD, which acknowledges the involvement of multiple mechanisms acting in concert in individuals with a genetic predisposition to develop the condition. These mechanisms include insulin resistance, adipose tissue hormones, nutritional factors, the gut microbiota, and genetic factors related to lipid metabolism. Furthermore, insulin resistance is believed to be the central pathogenic factor which implicates an imbalance between proinsulin (adiponectin) and anti-insulin cytokines (TNF- α), especially those produced by adipokines in adipose tissue. TNF- α levels increased in patients with NAFLD, whereas the opposite occurred with adiponectin levels [4-7].

NAFLD is a common liver disease, with a 25.24% global prevalence and a 27.37% incident rate in Asia. In Indonesia, the prevalence at 30.6%, which is higher compared of 24.6% and 20% in India and China, respectively [2,8].

The high prevalence of NAFLD in developing countries such as Indonesia is a significant concern. Additionally, NAFLD has been linked to cardiovascular diseases, including hypertension [9]. Hypertension is an early risk factor for various cardiovascular conditions, and The World Health Organization (WHO) reports a 31.1% prevalence of hypertension worldwide. Furthermore, based on data from Basic Health Research, approximately two-thirds of patients with NAFLD come from developing countries, including Indonesia. In 2018, Indonesia reported a high incidence rate of 34.1% for NAFLD [9].

Hypertension is a medical condition characterized by consistently elevated blood pressure (BP). According to the Global Hypertension Practice Guidelines established by the International Society of Hypertension (ISH) in 2020, hypertension is described as having a systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher [10]. Blood pressure is influenced by various cardiovascular parameters, including cardiac output and vascular resistance. These parameters, in turn, are affected by factors such as intravascular volume and the activity of the neurohumoral system. Blood pressure regulation comes from the complex interaction of various integrated neurohumoral system elements, such as the renin-angiotensin-aldosterone system (RAAS), the role endothelial natriuretic peptides, sympathetic nervous system (SNS), and the immune system, including inflammatory mechanisms [11].

NAFLD and hypertension are associated with hepatic lipotoxicity. The molecular pattern associated with damage by injured hepatocytes triggers an innate immune response and increases pro-inflammatory production, which can be released into the bloodstream, causing systemic inflammation. Earlier studies have indicated a connection between NAFLD and systemic inflammatory responses, which are indicated by high levels of IL-6 (interleukin 6), TNF- α (tumour necrosis factor α), and CCL2 (CC-chemokine ligand 2) [12]. Additionally, the secretion of hepatokines towards steatosis can contribute to systemic inflammation.

Inflammation plays a significant role in the development of hypertension, and strongly influenced by SNS activation. SNS activation leads to increased heart rate and the release of epinephrine and norepinephrine, ultimately contributing to hypertension [13]. Furthermore, inflammation can induce hypertension by activating the RAAS through hepatic stellate cell intermediaries. These activated stellate cells express RAAS components and increase the synthesis of angiotensin II, which promotes sodium and water retention and contributes to the development of hypertension [14].

This aligns with a study that reported a hypertension rate of 17.3% in patients with NAFLD. The incidence of hypertension was found to be significantly associated with the degree of steatosis. These findings highlight the progressive increase in hypertension incidence with the severity of steatosis [15-17].

Indonesia has a relatively high prevalence of NAFLD and hypertension. Moreover, hypertension is a major risk factor for cardiovascular disease, leading to death globally, claiming approximately 17.9 million lives annually [9]. However, only a few studies have explored the relationship between steatosis and hypertension. Therefore, this study investigated the correlation between the degree of hypertension and the degree of steatosis in patients with NAFLD at the Hajj Hospital Syarif Hidayatullah State Islamic University Jakarta, Indonesia.

2. MATERIAL AND METHODS

2.1. Study Design and Participant

This cross-sectional study was performed using a correlation approach that focused on two variable groups. The target population included patient with NAFLD at the Hajj Hospital Syarif Hidayatullah State Islamic University. A consecutive sampling method was used, where the sample was taken from the population that fulfilled the inclusion criteria and passed the exclusion criteria.

2.2. Sample size and measurement tools

The inclusion criteria were adult patients over 18 years old who were diagnosed with NAFLD through abdominal ultrasound examination and blood pressure measurement, as recorded in the medical records of the Hajj Hospital between 2019 and 2021.

Abdominal ultrasound examination used to identify NAFLD was based on B-mode two-dimensional ultrasound with grading based on liver echogenicity identification as well as intrahepatic vascular and diaphragm imaging, with grading values as follows [18]:

(1) Grade I or mild degree: slightly increased liver parenchymal echogenicity as well as clear diaphragm and intrahepatic vascular wall imaging.

(2) In cases of Grade II or moderate degree, the liver parenchyma exhibits increased echogenicity, and diaphragm or intrahepatic vascular wall imaging may appear less clear.

(3) Grade III or severe degree: Nearly complete increase in liver parenchymal echogenicity, loss of diaphragm and intrahepatic vascular imaging, and inadequate penetration in the posterior segment of the right liver lobe.

The normal liver texture appears homogenous, with good or isoechoic echogenicity compared to the normal renal cortex, and no posterior attenuation on ultrasound. The sonographic pattern consisted of 0 for homogenous and normal nodules, 1 for hyperechoic nodules, 2 for multiple confluent hyperechoic lesions, 3 for the absence of hypoechoic nodules, 4 for irregular hyperechoic and hypoechoic areas, and 5 for diffuse involvement.

The hypertension degree criteria used were adapted from the 2020 ISH Global Practice Guidelines [10].

The exclusion criteria were excessive alcohol consumption history according to the alcoholic fatty liver criteria (do not consume more than 60 g/day (male) and 40 g/day (female)), a history of diabetes, dyslipidemia, and obesity [2].

The correlation analysis formula determined the sample size estimation. A total of 53 subjects fulfilled the inclusion criteria established by this study. The results were processed using SPSS version 24.0 through Somers'd statistical test to identify the direction and strength of the correlation between the two variables. The association between independent and dependent variables was determined using P-values. A P-value less than 0.05 indicated a significant relationship between the independent and dependent variables. The study also assessed the characteristics of the subjects, including the proportion of steatosis degree and degree of hypertension in NAFLD.

2.3. Ethical Approval

This study followed the rules of the Indonesian Medical Ethics Guidelines was approved by the Medical Research Ethics Committee of the Faculty of Medicine, Syarif Hidayatullah State Islamic University, Jakarta (with registry number B-079/F12/KEPK/TL.00/11/2022). All data were kept confidential and use only for study purposes.

3. RESULTS

3.1. Characteristics of subject in NAFLD patients

In this study, the total number of subjects was 53, with 53% of them being above the age of 50. The average age of participants was 50.09 years. Among the different age groups, the highest proportion of NAFLD was found in the elderly group aged 61-70 years, accounting for 28.4%. In terms of sex distribution, females were the dominant group, comprising 30 subjects (56.6%) (Table 1).

Table 1. Characteristics subjects in NAFLD Patients

Age Group (years old)	Male		Female		Total (n=53)	
	N	%	N	%	N	%
0 – 20	0	0	1	1.9	1	1.9
21 - 30	3	5.6	3	5.6	6	11.2
31 – 40	2	3.7	4	7.6	6	11.3
41 – 50	10	18.9	2	3.7	12	22.6
51 – 60	4	7.6	9	17.0	13	24.6
61 – 70	4	7.6	11	20.8	15	28.4
Total sex	23	43	30	56	53	100%

Table 2 showed mild steatosis was observed in 29 patients (54.7%), while severe steatosis was present in only 3 patients (5.6%), indicating that mild NAFLD was the most common form in the population.

Table 2. The proportion of steatosis degree in NAFLD patients

Steatosis Degree	Frequency (n=53)	Proportion (%)
Mild	29	54,7
Moderate	21	39,7
Severe	3	5,6

3.2. The proportion of hypertension in NAFLD patients

Table 3 showed that the most common blood pressure was normal at 37.7% in NAFLD subjects, meanwhile, the proportion of prehypertension was 22.6%. This study showed that the proportion of hypertension (systolic ≥ 140 mmHg and diastolic ≥ 90 mmHg) in NAFLD patients was 21 subjects (39.7%), consisting of 28.4% with grade I hypertension and 11.3% with grade II hypertension.

Table 3 Proportion of hypertension in NAFLD patients

Blood Pressure Stage (SBP/DBP)	Frequency (n=53)	Proportion (%)
Normal <130/85 mm Hg	20	37.7
Normal-High (prehypertension_ 130-139/85-89 mm Hg	12	22.6
Grade I hypertension 140-159/90-99 mm Hg	15	28.4
Grade II hypertension $\geq 160/\geq 100$ mmHg	6	11.3

3.3. The characteristic subject of NAFLD patients with hypertension

Table 4 below showed that 61.9% of patients with NAFLD who had hypertension were aged 51- 60 years old. Table 4 also showed the proportion of females with age than 50 years old was dominant (42.85%).

Table 4. Characteristics subjects in NAFLD patients with hypertension

Age Group (years)	Male		Female		Total (n=21)	
	N	%	n	%	N	%
< 50	4	19.05	4	19.05	8	38.1
51 – 60	2	9.52	5	23.8	7	33.3
> 60	2	9.52	4	19.05	6	28.6
Total sex	8	38.1	13	61.9	21	100%

Furthermore, Table 5 indicated, that the systolic and diastolic means in mild NAFLD were 126±15 and 79±10 mmHg, respectively, while those in severe NAFLD were 150±14 mmHg and 97±10 mmHg, respectively. The mean blood pressure increased due to the severity of steatosis.

Table 5. Mean blood pressure based on steatosis degree of NAFLD patients

Steatosis Degree	Mean SBP (mmHg)	Mean DBP (mmHg)
Mild	126±15	79±10
Moderate	133±12	78±10
Severe	150±14	97±10
Overall	130	79

3.4. Correlation between the steatosis and hypertension degree in NAFLD patients

Table 6. Correlation between steatosis and hypertension degree in NAFLD patients

Degree of steatosis	Blood Pressure								R	P		
	Normal		Normal-High		Stage I Hypertensio		Stage II Hypertensio					
	N	%	N	%	n	%	n	%				
Mild	14	48.3	6	20.7	7	24.1		6.9%	29	54.7%	0.251	0.029
Moderate	6	28.6	6	28.6	8	38.1		4.7%	21	39.7%		
Severe	0	0.0	0	0.0	0	0.0		100%	3	5.6%		

Table 6 showed a significant correlation between hypertension and steatosis P=0.029, (P<0.05) and a correlation coefficient of r=0.251, indicating a weak correlation based on Somers'd test. Moreover, 31% of patients with mild NAFLD had hypertension, which increased by 42.8% in those with moderate NAFLD, and 100% of patients with severe NAFLD had stage II hypertension, as shown in (Table 6).

4. DISCUSSION AND CONCLUSION

In this study, 53% patients of NAFLD were above 50 years old, with a mean age of 50.09. This result was similar to Ng et al.study which reported a mean age of NAFLD patients at 52.57 years, while other studies, reported younger ages at 46 years and 43.6 years, respectively [16,17,19]. The highest proportion of NAFLD based on age group were elderly 61-70 years old (28.4%), while Duseja et al. suggested that NAFLD typically occurs during the fourth and fifth decades of life, with a peak incidence at 40-49 years in males and 50 years in females. However, separate studies in Indonesia indicated that NAFLD is more prevalent in the age range of 51-60 years [20,21].

This study also observed that 56.1% of the subjects were female. Other study in Indonesia such as Marina et al. noted that 56% of their subjects were female and identified a significant association between female and severity of NAFLD and also Rengkung, et al. reported a higher proportion of females, accounting for 67% of their study population [20,21].These findings support the theory proposed by other studies, which more commonly occurs in women, specifically those experiencing menopause, owing to the deficiency of anti-inflammatory oestrogen [5,20,22].

Our study showed the proportion of NAFLD in mild degrees 54.7%, moderate degree 39.7%, and severe degree 5.6 %. These results were rather different from Marina et al. who found the proportion of NAFLD patients was 42% in normal to a mild degree of steatosis and moderate degree at 34%, and severe degree at 24% [20]. While Ryoo et al. showed the distribution of NAFLD patients in Korea was very high in normal-mild degrees at 95.44%, moderate degrees at 4.45%, and severe degrees at 0.11%. Although our results differed from those other studies, all studies

had more populations with mild to moderate degrees of steatosis and less prevalent severe degrees of steatosis [21].

Proportion of hypertension patient with NAFLD patients was found to be 39.7% in this study. These findings were lower compared to the results reported by previous study who identified hypertension in 59.3% and 45.65% of the NAFLD population, respectively [16,17].

This study also showed that the proportion of pre-hypertension was 22.6%, grade I hypertension 28.4 % and grade II hypertension 11.3%. While study in Brazil revealed the proportions of NAFLD among individuals with normal blood pressure, pre-hypertension, and hypertension were 16.5%, 37.5%, and 59.3%, respectively. Furthermore, in multivariate analyses, prehypertension and hypertension were associated with an increased of NAFLD. The adjusted odds ratio for prehypertension was 1.3 (95% confidence interval 1.1-1.6), while for hypertension, it was 1.8 (95% confidence interval 1.4–2.3) [17].

Our study also revealed that the most common hypertension in patients with NAFLD was female and aged 50 years and older.

This result was consistent with the theory that lipotoxicity in hepatocytes induces RAAS through hepatic stellate cell pathway activation, which increases RAAS component expression, synthesizes angiotensin II, and induces sodium and water retention in the kidney tubules. Angiotensin II increases endothelial dysfunction, leading to elevated systemic vascular resistance [14]. Additionally, lipotoxicity induces pro-inflammatory cytokines and ROS (reactive oxygen species) in various organs, such as blood vessels and kidneys. Systemic inflammation can activate the SNS and increase catecholamine hormones, directly increasing mean arterial pressure (MAP) [13,23]. Hepatokines such as fetuin-A and retinol binding protein 4 (RBP4) increase in individuals with NAFLD, activating toll-like receptor 4 (TLR4) dependent proinflammatory pathways [23]. The increased fat deposition in hepatocytes has been attributed to several factors, including insulin resistance, lipotoxicity, and changes in gut microbiota, which could contribute to hepatic and extrahepatic complications [7,9].

Several epidemiological studies have concluded that NAFLD could increase all-cause mortality related to hypertension, CVD, hepatocellular carcinoma, diabetes mellitus, and renal and lung diseases. Ng et al. study showed hypertensive NAFLD significantly raised the all-cause and CVD mortality risk [16]. In addition, people with prehypertension and hypertension plus moderate/severe NAFLD had higher cardiovascular events (CVE) risks than those with normal BP and no NAFLD, respectively [24].

The overall mean blood pressure of all patients with NAFLD in this study was within the normal to high range of 130/79 mmHg. This finding is consistent with Li et al. who observed a mean blood pressure of 132/80 mmHg in their study population, while Aneni, et al. analyzed a mean blood pressure of 124/80 mmHg [18,24].

Similar with this study, previous studies found that a more severe degree of steatosis in patients with NAFLD may increase the degree of hypertension. Mean blood pressure of severe degree steatosis of this study was 150/97 mmHg, while study in China found moderate to severe steatosis had a mean systolic pressure of 136/84 mmHg [24]. Other study in Indonesia also showed that a mild degree of NAFLD is more frequent in the prehypertension population, moderate degree was more frequent in grade I hypertension and a severe degree was more frequent in grade II hypertension ($p < 0.001$) [20]. The mean blood pressure in this study was also quite different from reported by Ryoo et al. where the mean systolic and diastolic values based on the moderate to severe degree were 115 ± 10 mmHg and 76 ± 6 mmHg, respectively [15].

This study was observed difference in other study. It can be attributed to the study conducted by Ryoo, et al. was carried out in South Korea, a developed country with a lower incidence of hypertension. In contrast, study conducted in China obtained a result that closely aligned with our findings because of China is developing country similar to Indonesia [25]. These consistent with epidemiological studies conducted by the WHO that indicated that approximately two-thirds of individuals with hypertension reside in developing countries [9].

This study indicated a correlation between the degree of steatosis and hypertension due to increased blood pressure in line with the severity of NAFLD. The correlation was weak because hypertension was found mostly in patients with moderate steatosis, whereas severe NAFLD was found in less than 10% of the subjects. However, all the patients with severe steatosis had grade II hypertension. Similarly, Ryoo et al. reported that the incidence rate of hypertension increased with the severity of NAFLD. The incidence rates were as follows: normal group (14.4%), mild group (21.8%), and moderate to severe group (30.1%) ($P < 0.001$).

Clinical evidence has consistently indicated correlation between NAFLD and hypertension. Elevated blood pressure is associated with fatty liver disease and has the potential to contribute to the progression of liver fibrosis. However, that study focused solely on liver steatosis. Nevertheless, both epidemiological and experimental evidence support the notion that NAFLD is a multisystem disorder with systemic implications, such as inflammation, insulin resistance, oxidative stress, and hypertension. The interplay between NAFLD, the genome, epigenome, and the gut microbiome further support the role of NAFLD in the development and progression of hypertension. It is worth noting that hepatic steatosis is not benign, but may have more detrimental effects than visceral fat. RAAS drugs, including angiotensin converting enzyme (ACE) inhibitors such as captopril and ramipril, have been tested for NAFLD and have shown a favourable profile by reducing insulin resistance and the progression of fibrosis [14]. Therefore, further evidence is still needed, and patients with hypertension need to be considered and treated for fatty liver disease and vice versa [14]. Based on these results, it was suggested that patients with grade II hypertension should check for fatty liver and consider females aged ≥ 50 years to screen for fatty liver.

This study has limitations that only evaluated the correlation between hypertension and liver steatosis without consideration of diabetes, obesity, and dyslipidemia as familiar related to metabolic association fatty liver disease (MAFLD). Another limitation is that the assessment of the degree liver steatosis was solely conducted using abdominal ultrasound, rather than employing more precise methods such as liver biopsy or utilizing CAP scores through liver elastography techniques FibroScan or MRE.

In conclusion, the study conducted at Hajj Hospital Syarif Hidayatullah State Islamic University revealed that the proportion of hypertension patients with NAFLD was 39.7%. Majority of patients were 61% in aged 50 or older and predominantly female. Furthermore, most patients with NAFLD had a mild degree of steatosis. Additionally, 28.4% of the patients had stage I hypertension, whereas 11.3% had stage II hypertension.

A weak correlation was observed between the degree of steatosis and the degree of hypertension in patients with NAFLD. These results were due to patients being dominated by moderate steatosis and normal to high and grade I hypertension. However, all the patients with grade II hypertension had severe steatosis.

Because of hypertension, patients with NAFLD should be treated by a multidisciplinary team to obtain longitudinal results. Hypertension development is more related to progressive NAFLD, moderate and severe degrees, than to normal or milder degrees. NAFLD was an independent risk factor for hypertension. Based on these results, it was suggested that females aged ≥ 50 years and patients with grade II hypertension should be screened for fatty liver.

Moreover, further studies with larger populations are recommended to determine the correlation between steatosis or fibrosis and the degree of hypertension and other risk factors (diabetes, dyslipidemia, and obesity) using liver elastography or MRE.

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Author contribution

FNA and HH, the main supervisors, contributed to the design and implementation of the study. FNA, HH, PDB and RAA designed and directed the study; gathered, arranged, and examined the data; and wrote the initial,
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second, and final manuscript drafts. RAA and PDB contributed to data collection. All authors critically reviewed and approved the final draft and were responsible for the content and similarity index.

CONFLICT OF INTEREST

The author (s) declare no potential conflicts of interest concerning the research, authorship, and publication of this article.

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