Ultrasound-Diagnosed Non-Alcoholic Fatty Liver Disease among Medical Check Up Patients

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ABSTRACT

Background: *Non-alcoholic fatty liver disease (NAFLD) is recognised as one of the most important causes of chronic liver disease and has become an important health issue in many countries. The aim of the study was to evaluate the prevalence and risk factors of NAFLD patients based on ultrasound diagnosed in medical check up setting.*

Method: *In this study, of 2,105 patients undergoing medical check up in Charitas Hospital, Palembang between January 2011 to August 2013, 115 NAFLD patients and 113 non-NAFLD patients as controls were included. Diagnosis of NAFLD was based on ultrasound appearance, patients did not consume alcohol, with negative HBsAg and hepatitis C virus antibodies.*

Results: *The prevalence of NAFLD in medical check up patients was 7.9% whereas 39% patients had normal body mass index (BMI) (< 25 kg/m^2). Patients with NAFLD compared with non-NAFLD patients had higher values of BMI ($p < 0.001$), triglycerides ($p = 0.001$), aspartate aminostransferase (AST) ($p < 0.001$), alanine aminotransferase (ALT) ($p < 0.001$), fasting glucose ($p = 0.002$), and lower HDL cholesterol ($p = 0.001$). Obesity was the strongest associated factor for NAFLD (95% CI = 1.87-7.85; OR = 3.83; $p < 0.001$), followed by high glucose levels (95% CI = 1.38 - 8.31; OR = 3.83; $p = 0.008$) and hypertriglyceridemia (95% CI = 1.38 - 4.11; OR = 2.38; $p = 0.002$).*

Conclusion: *About 7.9% patients suffered from NAFLD. Approximately 39% medical check up patients had NAFLD with normal BMI. Obesity, hypertriglyceridemia and high glucose levels were the risk factors for NAFLD.*

Keywords: *non-alcoholic liver disease, body mass index, prevalence, metabolic syndrome*

ABSTRAK

Latar belakang: *Penyakit perlemakan hati non alkoholik (PPHNA) merupakan salah satu penyebab terpenting penyakit hati kronis dan telah menjadi masalah kesehatan di berbagai negara. Tujuan dari penelitian ini adalah untuk mengetahui prevalensi dan faktor risiko PPHNA yang didiagnosis berdasarkan pemeriksaan ultrasonografi pada pemeriksaan medical check up (MCU).*

Metode: *Dalam penelitian ini, dari 2.015 pasien yang menjalani MCU di Rumah Sakit Charitas, Palembang selama periode Januari 2011 hingga Agustus 2013, dilibatkan sejumlah 115 pasien penderita PPHNA dan 113 pasien non-PPHNA sebagai pembanding. Diagnosis PPHNA berdasarkan pada pemeriksaan ultrasonografi, pasien bukan peminum alkohol, HBsAg dan anti hepatitis C virus negatif.*

Hasil: *Angka prevalensi PPHNA adalah 7,9% dimana sejumlah 39% pasien PPHNA memiliki indeks massa tubuh normal (25 kg/m^2). Pasien dengan PPHNA dibandingkan yang pasien non-PPHNA mempunyai nilai lebih tinggi secara bermakna pada indeks massa tubuh ($p < 0,001$), kadar trigliserida ($p = 0,001$), aspartate aminotransferase (AST) ($p < 0,001$), alanin aminotranferase (ALT) ($p < 0,001$), gula darah puasa ($p = 0,002$), dan memiliki kadar kolesterol HDL lebih rendah ($p = 0,001$). Obesitas merupakan faktor risiko terkuat terjadinya*

PPHNA (95% CI = 1,87–7,85; OR = 3,83; p < 0,001), diikuti peningkatan kadar glukosa (95% CI = 1,38–8,3; OR = 3,83; p = 0.008) dan hipertrigliseridemia (95% CI = 1,38–4,11; OR = 2,38; p = 0,002).

Simpulan: *Prevalensi pasien dengan PPHNA adalah 7,9%. Sejumlah 39% pasien PPHNA mempunyai indeks massa tubuh normal. Obesitas, hipertrigliseridemia dan kadar gula darah tinggi merupakan faktor risiko terhadap PPHNA.*

Kata kunci: *penyakit perlemakan hati non alkoholik, indeks massa tubuh, prevalensi, sindrom metabolik.*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the hepatic pandemic of the 21st century, being the number one cause of chronic hepatic disease in the occidental world. Although usually benign, fatty liver may be associated with serious injury, inflammation and hepatocyte necro-apoptosis, non-alcoholic steatohepatitis (NASH) in 20–30% of subjects. Those patients are at risk of developing fibrosis, with one fifth progressing to liver cirrhosis.[1] The definition of non-alcoholic fatty liver disease (NAFLD) requires: (a) presence of evidence of hepatic steatosis, either by imaging or histology, and (b) absence of causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia.[2]

Histologically, NAFLD is further catagorized into non-alcoholic fatty liver which there is the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes, and non-alcoholic steatohepatitis (NASH). NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.[1,2] The prevalence of NAFLD in adults is about 20% and the prevalence of NASH is 2-5%.[3]

The diagnosis of NAFLD requires a combination of invasive and non-invasive test. Liver biopsy is considered the gold standard for definitive diagnosis of NAFLD. The most frequent and readily available method to measure hepatic steatosis is by ultrasonography (USG). The overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of ultrasound for the detection of moderate-severe fatty liver, compared to histology (gold standard) were 84.8%, 93.6%, 13.3 and 0.16, respectively.[4] The aim of the study was to evaluate the prevalence and risk factors of NAFLD patients based on ultrasound diagnosed in medical check up setting.

METHOD

From January 2011 to August 2013, there were 2,105 patients undergoing medical check up in Charitas Hospital, Palembang. Sociodemographic characteristics (age and sex), medical history (alcohol consumption, smoking habits, past history of chronic liver disease, hypertension, stroke, diabetes mellitus, coronary arterial disease), anthropometric measurement (weight, height, body mass index (BMI), blood pressure) and laboratory data (blood sugar, total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV) were recorded.

The abdominal ultrasonography was performed, and the presence of fatty liver was defined as the increased echogenicity of the hepatic parenchyma (longitudinal sonogram of the right lobe of the liver and right kidney shows increased overall echogenicity of the liver) and posterior attenuation.[5] Each patient was submitted to an abdominal ultrasound examination with Aloka Model SSD-3500 Prosound, using 3.5 MHz convex probe. National Institute of Health defined BMI was considered as obesity (BMI $\geq$ 30 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and normal (BMI < 25 kg/m^2).[6] Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program: Adult Treatment Panel III.[7] In particular, patients were considered to have metabolic syndrome, if they met three or more of the following criteria: (1) increased waist circumference > 102 cm for males or > 88 cm for females; (2) high triglyceride levels $\geq$ 150 mg/dL; (3) low HDL cholesterol < 40 mg/dL for males and $\geq$ 150 mg/dL for females; (4) fasting plasma glucose $\geq$ 110 mg/dL or previously diagnosed type 2 diabetes mellitus; (5) elevated arterial pressure: systolic $\geq$ 135 mmHg and/or diastolic $\geq$ 85 mmHg or previously diagnosed hypertension. Waist circumference examination was not routinely done in Charitas Hospital, so this parameter was replaced by BMI > 30 kg/m^2.

Adults of both sexes from the Charitas Hospital who came to the hospital for medical check up, between the ages 15–80 years old who had been confirmed to have fatty liver by ultrasonography were included. Patients were not included in the study if they had history of alcohol intake, presence of chronic liver disease, presence of the HBsAg or the presence of HCV antibodies.

Quantitative data were expressed as mean values ± standard deviation. The normality of distribution of continuous quantitative variables was tested using the Kolmogorov-Smirnov test. Comparisons between groups of quantitative variables with normal or abnormal distribution were performed using T-test or Mann-Whitney test, respectively. Comparison of categorical or prevalence were performed using Chi-square test. A two tailed $p < 0.05$ was considered to be statically significant. All analysis was carried out using the SPSS 17.0.

RESULTS

From January 2011 to August 2013, there were 2,105 patients undergoing medical check up in Charitas Hospital, Palembang. Based on liver ultrasound, there were 166 (7.9%) patients diagnosed as NAFLD, but only 115 patients were included in this study because of missing data and 113 patients with normal ultrasound (non–NAFLD) were recruited as control.

The majority (81.1%) of the patients was male, which was more common to suffer from NAFLD than female patients. The average age of the NAFLD patients were 43.38 ± 9.26 year old and NAFLD patients were older than non-NAFLD patients ($p = 0.005$).

Patients with NAFLD compared with non-NAFLD patients had higher values of BMI (27.72 ± 4.61 vs. 24.92 ± 4.02; $p < 0.001$), triglycerides (170 ± 101 mg/dL vs. 128 ± 84 mg/dL; $p = 0.001$), AST (27.35 ± 10.06 IU/L vs. 22.52 ± 9.90 IU/L; $p < 0.001$), ALT (45.45 ± 24.11 IU/L vs. 29.92 ± 42.66 IU/L; $p < 0.001$), fasting glucose (101.64 ± 31.33 mg/dL vs. 91.68 ± 22.90 mg/dL; $p = 0.002$), and had lower HDL cholesterol (47.29 ± 18.50 mg/dL vs. 52.15 ± 14.52 mg/dL; $p = 0.001$) (Table 1). In this study, ALT and AST levels increased in 34.7 % and 9.6% of NAFLD patients, respectively. The prevalence of the metabolic syndrome according to presence of NAFLD and BMI criteria was shown in Table 2 and 3. According to metabolic syndrome criteria, NAFLD patients compared to non-NAFLD patients were more obese (31.30 % vs. 10.62 %; p

Table 1. Clinical and laboratory data of the patients

Characteristics	Total n (%)	Non-NFALD n (%)	NFALD n (%)	p
Sex				
Male	185 (81.1%)	85 (75.2%)	100 (87 %)	0.028
Female	43 (18.9%)	28 (24.8%)	15 (13 %)	
Age (years)	41.57 ± 9.76	39.73 ± 9.94	43.38 ± 9.26	0.005
BMI (kg/m^2)	26.33 ± 4.54	24.92 ± 4.02	27.72 ± 4.61	< 0.001
SBP (mmHg)	119.30 ± 13.02	118.63 ± 12.87	119.96 ± 13.19	0.300
DBP (mmHg)	77.87 ± 7.08	77.21 ± 6.84	78.52 ± 7.28	0.169
Cholesterol (mg/dL)	207.10 ± 38.06	202.60 ± 36.19	211.52 ± 39.47	0.103
HDL-C level (mg/dL)	49.70 ± 16.79	52.15 ± 14.52	47.29 ± 18.50	0.001
Triglyceride (mg/dL)	149.63 ± 95.41	128.63 ± 84.27	170.27 ± 101.39	0.001
LDL (mg/dL)	139.97 ± 34.23	136.03 ± 33.30	143.84 ± 34.82	0.085
AST (IU/L)	24.95 ± 10.25	22.52 ± 9.90	27.35 ± 10.06	< 0.001
ALT (IU/L)	37.76 ± 35.36	29.92 ± 42.66	45.45 ± 24.11	< 0.001
Fasting glucose (mg/dL)	96.71 ± 27.87	91.68 ± 22.90	101.64 ± 31.33	0.002

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; AST: aspartate aminotransferase; ALT: alanin transaminase

Table 2. NAFLD patients and non-NAFLD patients according to metabolic syndrome criteria

Disorder	Total (n = 228)		p
	Non-NAFLD (n = 113)	NAFLD (n = 115)	
Obese	12 (10.62%)	36 (31.30%)	0.001
Hypertriglyceridemia	33 (29.20%)	57 (49.57%)	0.002
Low HDL-C	21 (18.58%)	31 (26.96%)	0.133
Hypertension	14 (12.39%)	23 (20.0%)	0.120
High glucose	7 (6.19%)	22 (19.13%)	0.006
Metabolic syndrome	2 (1.77%)	8 (7.0%)	0.056

NAFLD: non-alcoholic fatty liver disease; HDL: high density lipoprotein

= 0.001), more hypertriglyceridemia (49.57% vs 29.20%; p = 0.002), and higher glucose levels (19.13% vs. 6.19%; p = 0.006). (Table 2). The prevalence of metabolic syndrome (more than 3 criteria) was 7% in NAFLD patients and 1.77% in non-NAFLD patients (p = 0.056).

The prevalence of NAFLD patients with normal BMI (< 25 kg/m^2) was 39.13%. In the normal weight group, the prevalence of hypertriglyceridemia and high glucose levels were significantly more frequent in the NAFLD patients than in non-NAFLD patients. In the overweight and obese group (BMI > 25 kg/m^2), the prevalence of hypertriglyceridemia, low HDL-C, hypertension, high glucose and metabolic syndrome were more frequent but not significant in NAFLD patients compared to non-NAFLD patients (Table 3). Table 4 showed the risk factors for NAFLD. Obesity was the strongest associated factor for NAFLD (95% CI = 1.87-7.85; OR = 3.83; p < 0.001), followed by high glucose levels (95% CI = 1.38-8.31; OR = 3.83; p = 0.008) and hypertriglyceridemia (95% CI = 1.38-4.11; OR = 2.38; p = 0.002).

DISCUSSION

The reported prevalence of NAFLD varies widely depending on the population studied and the definition used. Fan et al reported that the prevalence of NAFLD in a general population of Shanghai, China was 17.2%.[8] In a study consisting of nearly 400 middle age individuals, the prevalence of NAFLD defined by USG was 46% and the prevalence of histologically confirmed NASH was 12.2%.[9] The prevalence of NAFLD in those patients attending the routine health checkup was 22.6%.[10] Generally, prevalence of NAFLD among the adult population of Asia-Pasific countries varied from 5% to 30%.[11,12] In Indonesia the prevalence was 30%.[13] In this study, we found that the prevalence of NAFLD was 7.9%. According to ultrasonography examination, degree of severity of fatty liver was classified into three categories: mild, moderate and severe. By this category, Martina et al reported the prevalence of NAFLD was 82.9%.[14] While in this study, the radiologist used severe criteria (marked increased in echogenicity, poor penetration of the of the posterior segment of the right hepatic lobe and poor or no visualization of the hepatic vessels and diaphragm) in diagnosis of NAFLD.[14]

Mild to moderate elevation of serum aminotransferases (ALT and AST) is the most common and often the only laboratory abnormality found in patients with NAFLD.[15] In this study, patients with NAFLD showed elevation of transaminase enzyme, there were ALT 34.7% and AST 9.6%. Study by Fu et al showed that among 86 adolescents with fatty liver, only 20 (23.3%) showed abnormality for ALT, however, there was an increasing trend of ALT abnormality as the severity of fatty liver increased.[16]

The association of NAFLD with obesity and metabolic syndrome are well established in both Caucasians and Asians. In our study the prevalence of normal BMI in NAFLD patients was 39%. This prevalence is higher than the other studies. Ekaterini et al showed that the prevalence of NAFLD patients with normal BMI was 12% and Deepa et al reported normal BMI was present in 21.7%.[10,17] In our study the prevalence was 31.3% meanwhile the prevalence of NFLD in obese patients varied from 10–80%.[11] Radu et al reported that metabolic syndrome was found in 61.09% of patients with NAFLD and in the United States was 22% in the general population.[18] Central obesity is a mandatory condition for the metabolic syndrome. In patients with NAFLD had in percentage of central obesity, even in the presence

Table 3. Prevalence of metabolic disorders according to body mass index

Characteristic	Normal weight		p	Over weight and obese		p
	Non-NAFLD n = 56 (60.86%)	NAFLD n = 36 (39.13%)		Non-NAFLD n = 57 (41.91%)	NAFLD n = 79 (58.09%)	
Hypertriglyceridemia	12 (21.43%)	19 (52.78%)	0.002	21 (36.84%)	38 (48.10%)	0.193
Low HDL-C	8 (14.29%)	8 (22.22%)	0.330	13 (22.80%)	23 (29.11%)	0.412
Hypertension	2 (3.57%)	5 (13.89%)	0.070	12 (21.05%)	18 (22.78%)	0.811
High glucose	2 (3.57%)	6 (16.67%)	0.030	5 (8.77%)	16 (20.25%)	0.069
Metabolic syndrome	0 (0%)	2 (5.56%)	0.076	2 (3.51%)	6 (7.59%)	0.319

NAFLD: non-alcoholic fatty liver disease; HDL: high density lipoprotein

Table 4. Risk factors for non-alcoholic fatty liver disease

Risk factors	Odds ratio	95% CI	p
Obese	3.83	1.87–7.85	< 0.001
Hypertriglyceridemia	2.38	1.38–4.11	0.002
High glucose	3.38	1.38–8.31	0.008

of normal weight.[18] In our study the prevalence of metabolic syndrome in NAFLD patients was low (7%). Although the prevalence of metabolic syndrome was low, 49.57% of NAFLD patients fulfilled at least one criteria. Limitation of this study was that all patients who came for medical check up did not undergo waist circumference examination. According to the metabolic syndrome criteria there are five criteria; but in this study, waist circumference was not included and replaced by obese criteria (BMI > 30 kg/m^2). This could be the reason why the prevalence of metabolic syndrome was lower compared to other studies. Xiaona et al showed in their study that metabolic factors could increase the risk of NAFLD up to 1.5 - 3.8 times.[19] In our study, obesity, hypertriglyceridemia, and high glucose levels were the risk factors for NAFLD. It is appropriate with the concept that in the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia.[2]

CONCLUSION

This study showed that the prevalence of NAFLD and metabolic syndrome patients in medical check up setting was lower than others study. It is better for clinicians to also give attention to normal weight patients, because the prevalence of NAFLD patients with normal BMI was quite high. Obesity, hypertriglyceridemia and high glucose levels were risk factors for NAFLD.

REFERENCES

1. Mariana VM, Helena CP. Non-invasive diagnosis of non-alcoholic fatty liver disease a practical appraisal. J Hepatol 2013;58;1007-19.
2. Chalasani N, Younossi Z, Lavine JE, Anna MH, Elizabeth M, Brunt MD, Kenneth C, et al. AASLD Practice Guideline. The diagnosis and management of non-alcoholic fatty liver diasease: practice guideline by American Association for the Study of Liver Disease, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005-23.
3. Farrell GC, Larter CZ. Non-alcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006;43:S99-S112.
4. Ruben H, Lazo M, Susanne B, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011;54:1082-90.
5. Tchelepi H, Ralls PW, Radin R, Grant E. Sonography of diffuse liver disease. J Ultrasound Med 2002;21:1023-32.
6. National Institute of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults - the evidence report. Obes Res 1998;6 Suppl 2:51S-209S.
7. National Cholesterol Education Program. Executive summary: detection, elevation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486 -97.
8. Fan JG, Zhu J, Li XJ, Chen L, Li L, Dai F, et al. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. J Hepatol 2005;43:508-14.
9. William CD, Stenger J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of non-alcoholic fatty liver disease and non-alcoholic steatotohepatitis among a largely middled-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140:124–31.
10. Deepa U, Pipalia D, Chawla M, Patel R, Sonali M, Narayani, et al. Non-alcoholic fatty liver diasese (NAFLD), the hepatic component of metabolic syndrome. JAPI 2009;57:201-4.
11. Amarapurkar D, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pasific region and there local differences?. J Gastroenterol Hepatol 2007;22: 788-93.
12. Kamran BL, Fariborz G, Mojtaba M, Mehrzad L, Nima Z, Sayed TH, et al. Non-alcoholic fatty liver disease in Southern Iran: a population based study. Hepat Mon 2013;13:e9248.
13. Hasan I, Gani RA, Mahmud R. Prevalence and risk factors for non-alcoholic fatty liver disease in Indonesia. J Clin Gastroenterol Hepatol 2002;17(Suppl):S154.
14. Martina G, Diana ZB, Jesus CR, Jorge EP. Prevalence of non-alcoholic fatty liver disease in subjects with metabolic syndrome. Cir Cir 2012;80:122-26.
15. David A, Parke C, Kapil C. Nonalcoholic fatty liver disease: a clinical review. Dig Dis Sci 2005;50:171-80.
16. Fu CC, Chen MC, Li YM, Tso Tl, Li YW. The risk factors for ultrasound-diagnosed non-alcoholic fatty liver disease among adolescents. Ann Acad Med Sing 2009;38:15-21.
17. Ekaterini M, Melani D, Spillios M, George VP. Non-alcoholic fatty liver disease may develop in individuals with normal body mass index. Annals Gastroenterol 2012;25:45-51.
18. Radu C, Grigorescu M, Crisan D, Lupsor M, Constantin D, Dian L. Prevalence and associated risk factors of non-alcoholic fatty liver disease in hospitalized patients. J Gastrointestin Liver Dis 2008;3:225-60.
19. Xiaona H, Yiqin H, Zhijun B, Yiqian W, Dongmei S, Fang L, et al. Prevalence and factors associated with non-alcoholic fatty liver disease in Shanghai work-units. BMC Gastroenterol 2012;12;123-31.

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