IJPHCS
Open Access: e-Journal

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol 6:No. 4
July/August 2019

PREVALENCE OF FATTY LIVER CHANGES ON NON-CONTRAST ENHANCED COMPUTED TOMOGRAPHY AND ITS ASSOCIATED RISK FACTORS

Hasyma Abu Hassan[1*], Subapriya Suppiah[1,2], Choo Teen Koh[3], Laila Mastura Apandi[1], Ezamin Abdul Rahim[1]

[1]Department of Imaging, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia.
[2]Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia
[3]Department of Radiology, Hospital Sultan Ismail

**Corresponding author: Dr Hasyma Abu Hassan, Department of Imaging, Faculty Of Medicine & Health Sciences, Universiti Putra Malaysia.*
Email: hasyma@upm.edu.my

https://doi.org/10.32827/ijphcs.6.4.68

ABSTRACT

Background: The Fourth National Health and Morbidity Survey completed in 2011, revealed that 27.2% of Malaysian adults aged 18 years and above are obese, while 33.3% are pre-obese, with increasing prevalence of obese children. Together with observation of "ethnic lipodystrophy" in South Asians population and increasing prevalence of non-alcoholic fatty liver disease (NAFLD) in Asian population, further study of NAFLD in Malaysian population with their associated risk factors is necessary.

Materials and Methods: A prospective cross-sectional study of patients who underwent CT Urography (CTU) examination, selected through simple random sampling. Presence of NAFLD was determined based on liver CT value of <40 HU and CT Liver-Spleen attenuation ratio. Association and correlation of NAFLD with Body Mass Index (BMI), abdominal wall subcutaneous fat thickness and biochemical markers were calculated.

Result: Forty-six percent (46%) of study population had NAFLD, with male predominance. There were significant association of NAFLD with BMI, abdominal wall subcutaneous fat thickness and lower serum HDL level.

Conclusion: Increasing prevalence of NAFLD with increasing BMI, thicker abdominal wall subcutaneous fat thickness and decreasing serum HDL level

Keywords: non-alcoholic fatty liver disease, risk factors, non-contrast enhanced CT, subcutaneous wall thickness

1.0 INTRODUCTION

As South Asians were found to have a preponderance of adipocyte hypertrophy, lower adiponectin, reduced superficial subcutaneous fat, increased secondary storage in deep and visceral fat, and higher levels of ectopic fat deposition in the liver compared to people of European origin, an observation consistent with an ‘‘ethnic lipodystrophy’’ was made (Anand et al., 2011). The presence of abdominal obesity and associated cardio-metabolic risk factors including elevated insulin, low HDL, or low adiponectin, particularly in South Asian patients, should prompt clinicians to assess the patient for the presence of fatty liver, and prescribe health behavioural changes and medical therapy to try and normalize their risk factor profile (Anand et al., 2011).

According to WHO Expert Consultation (2004) (WHO Expert Consultation, 2004), recommended BMI cut-off points for body weight classification and public health action for Asians should be lower than the current WHO recommendation as Asians generally have a higher percentage of body fat than white people of the same age, sex, and BMI. Furthermore, greater proportion of Asian people below the existing WHO BMI cut-off point of 25 kg/m2, have risk factors for type 2 diabetes and cardiovascular disease. Therefore, those with BMI of 23 kg/m2 should be considered overweight in Asian population, while those with BMI of 27.5 kg/m2 and above should be considered obese.

The Fourth National Health and Morbidity Survey completed in 2011, revealed that 27.2% of Malaysian adults aged 18 years and above are obese, while 33.3% are pre-obese (NHMS, 2011). Another concerning factor which was revealed in the Survey, 3.9% of children below 18 years old, are also obese, based on weight for age status.

In a 4 years study done by Gaba et al. (2012) with 143 subjects, they showed that there was increasing incidence of hepatic steatosis with increasing weight (Gaba et al., 2012). BMI and the anterior subcutaneous fat thickness (Ant SQ) had a moderate correlation with the presence of liver steatosis (both $P<0.001$). The posterolateral subcutaneous ($P = 0.21$), posterior subcutaneous ($P = 0.001$), and intra-abdominal ($P = 0.010$) fat thicknesses demonstrated weak correlation with the presence of liver steatosis, as did the right ($P = 0.114$) and left ($P = 0.151$) hepatic lobe parenchymal densities. In addition, BMI was strongly correlated with the Ant SQ ($P < 0.001$).

Our study assessed the CT attenuation value of liver density in non-alcoholic fatty liver disease in correlation with body mass index and body fat measurements.

2.0 MATERIALS AND METHODS

This was a prospective cross-sectional study of patients who underwent CT Urography (CTU) examination for detection of urinary tract calculi within the study period from May 2013 till Dec 2014. The subjects were recruited through simple random sampling. These patients underwent interview, anthropometric (weight and height) measurement on the same day as CTU examination, and blood investigations (i.e. serum ALT, serum AST, lipid profile, fasting blood glucose, hepatitis screening) within 2 weeks of the CTU examination. BMI of the

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol 6:No. 4
July/August 2019

patients were calculated from the weight and height measurements. Written informed consent were obtained from all subjects who were eligible and agreeable for the study.

A total of 139 who fulfilled the inclusion criteria were recruited. Patients who consumed more than two standard drinks on any day or more than four standard drinks on a single occasion, who had had other known liver pathology or history of previous chemotherapy and radiotherapy were excluded from the study. Subjects who were on medications which may induce fatty liver such as amiodarone, methotrexate, diltiazem, expired tetracycline, antiretroviral therapy, glucocorticoids and tamoxifen were also excluded from the study.

Two independent examiners blinded to each other's findings and the patients' anthropometric measurements and laboratory data were recruited to review the CTU images for presence of fatty liver disease electronically via Picture Archiving and Communications System (PACS). Any disagreement will be settled by consensus. Images from CTU examination were used for measurements of the subcutaneous fat thickness in the abdominal wall, including Ant SQ and Pu SQ. The subcutaneous fat is defined as the distance from the skin to the body musculature. Measurements for the Ant SQ are taken at the level of the right renal hilum; and for the Pu SQ are taken at the paraumbilical region (Figure 1).

Figure 1. Measurement Locations: Paraumbilical Subcutaneous Fat Thickness (Pu) (A), and Anterior Subcutaneous Fat Thickness (a) at the level of right renal hilum (B).

The liver parenchymal density in Hounsfield units was measured on the CTU images using single-slice standard region-of-interest method to sample homogeneous areas representative of the parenchyma. Care was taken to avoid inclusion of vessels, bile ducts, focal changes of fatty liver or fatty sparing, and the surface margins.

After the normality test that confirmed the data was normally distributed, the analysis was run using parametric test. The patients' demographic information and presence of fatty liver disease using CT fat measurements of CT liver attenuation value were expressed in percentages. The Pu SQ, Ant SQ, BMI and laboratory results were expressed as mean ± standard deviation (SD) and range.

Pearson correlation coefficient was used to analyse the correlation between CT liver attenuation value with Ant SQ, Pu SQ and BMI. The strength of correlation was categorized according to the absolute R value of: 0.00 – 0.19 (very weak), 0.20 – 0.39 (weak), 0.40 - 0.59 (moderate), 0.60 – 0.79 (strong) and 0.80 – 1.0 (very strong).

Subjects were divided into 2 groups, namely, NAFLD and non-NAFLD based on the CT fat measurement with CT attenuation value of liver density. Univariate analysis - Independent samples T-test was used to test if there was a difference in the selected variables of scale parameters between the NAFLD and non-NAFLD group.

Univariate analysis using cross-tabulation with the Chi-square and fisher exact test were used to study the association between the NAFLD and the associated categorical variables, namely, the gender, race, hyperlipidemia, hyperuricaemia, BMI, Inc Ant SQ, Inc Pu SQ, and medical history of HT, DM and hyperlipideamia. A value of $P<0.05$ was considered statistically significant. Table 1 gives the definition of the categorical variables.

This study was approved by local medical research and ethics committees: National Medical Research Register (NMRR) and Medical Research Ethics Committee (MREC) [NMRR ID: NMRR-13-936-15989].

Table 1: Definition of the categorical variables

Categorical group	Definition	Value	Normal level	Unit
Hyperlipidemia	High TC	>5.17	0-5.17	mmol/L
	High LDL	>3.37	0-3.37	mmol/L
	High TG	>1.7	0-1.7	mmol/L
NAFLD	Liver and spleen ratio	<1.0	>1.0	HU (Hounsfield units)
	Liver CT attenuation value	<40	55 (Mean)	

Hyperuricaemia	High SUA	>420	210-420	umol/L
Inc Ant SQ	Increased Anterior abdominal subcutaneous thickness	≥24		mm
Inc Pu SQ	Increased Paraumbilical subcutaneous thickness	≥ 21.4 l		mm

3.0 RESULTS

3.1 Study demography

Of the 139 patients, 91 (65.5%) were male and 48 (34.5%) were female. The patients' age ranged from 15 to 84 with the mean of 53.48 years old. They comprised of Malay (65.5%), followed by Chinese (19.4%), Indian (13.7%) and others (1.4%).

3.2 Body Mass Indices of study population

The BMI of the study population ranges from 14.11 to 44.10, with the mean value of 26.50 and standard deviation (SD) of 5.39. Majority of subjects (61.8%) had high body mass index (BMI); with 53 (38.1%) overweight patients and 33 (23.7%) obese patients. About 1/3 of patients (32.4%) were within normal BMI range and there were approximately 6% of underweight patients.

3.3 Abdominal wall thickness

The Ant SQ of our patients ranges from 3.5mm to 58.20mm with mean of 23.94 ± 9.61. The Pu SQ ranges from 3mm to 66.10mm with mean of 27.73 ± 9.8. There were 60 patients (43.2%) with increased Ant SQ and 79 patients (56.8%) without increased Ant SQ. While 24.5% subjects showed increased Pu SQ as opposed to 73.4% with normal Pu SQ.

3.4 Prevalence of underlying co-morbidity

The majority of our patients (81 patients, 58.3%) was hypertensive on medications, while 53 patients (38.1%) had diabetes mellitus on medications and 72 patients (51.8%) had hyperlipidemia.

3.5 CT Liver Attenuation Value and Liver-Spleen Attenuation Ratio

The average CT liver attenuation value ranged from 12.40 to 72.20 HU with mean of 45.10 ± 12.75 HU. The average CT spleen attenuation value ranged from 34.60 to 62.10 HU with mean of 46.20 ± 5.19 HU. The mean of Liver-spleen attenuation ratio was 0.98 ± 0.28 with the minimum value of 0.27 and maximum value of 1.73.

3.6 Association between Average CT Liver Attenuation Value and BMI

There was inverse correlation between the CT attenuation value of the liver density and BMI whereby the CT attenuation value of the liver density was lower in higher BMI patients. The average and distribution of CT liver attenuation value was generally lower in the subgroup of obese patients compared with the control group.

3.7 Association between Average CT Liver Attenuation Value and Abdominal Wall Thickness

There was also an inverse correlation between the CT liver attenuation value and abdominal subcutaneous wall thickness where the CT attenuation value of the liver density was lower in thicker subcutaneous wall thickness, for both anterior (Ant SQ) and paraumbilical regions (Pu SQ). We observed that the mean and distribution of CT attenuation value of the liver density was lower in the group of patients with increased Ant SQ of ≥ 24mm and increased Pu SQ of ≥ 21.4mm.

3.8 Correlation between CT Liver Attenuation Value with the Ant SQ, Pu SQ and BMI

There was a significant ($p < 0.001$) inverse correlation between CT Liver Attenuation Value with the Ant SQ, Pu SQ and BMI. Pearson Coefficient analysis showed weak correlation between Ant SQ, Pu SQ and BMI with CT liver attenuation value ($r = -0.286$, $r = -0.297$, $r = -0.328$ respectively).

3.9 Prevalence and demographic data of NAFLD

The prevalence of NAFLD in general was 46% (64 patients) and non-NAFLD was 54% (75 patients). There were 20 (31.25%) female patients and 44 (68.75%) male patients with NAFLD. The mean age of patients with NAFLD was 52.45 ± 13.725 years (range 17-76 years). The ethnicity distribution was represented by Malay 68.75%, Chinese 12.5% and Indian 18.75%.

3.10 Association between NAFLD and Abdominal Wall Thickness

There were 56.25% of patients with increased Ant SQ in the NAFLD versus 32% in the non-NAFLD, p=0.004. There were 89.06% of patients with increased Pu SQ in the NAFLD versus 63.9% in the non-NAFLD, p<0.001. The Ant SQ and Pu SQ of the NAFLD group were thicker than the non-NAFLD. The mean of Ant SQ was higher in the NAFLD group (26.72 ±10.19 vs. 21.46 ± 8.61, p=0.002). The mean of Pu SQ was also higher in the NAFLD group (31.54 ± 9.81 vs. 24.33 ± 8.61, p<0.001).

Table 2: Mean of Anthropometric in NAFLD and Non-NAFLD

	NAFLD (N=64)	Non-NAFLD (N=75)	p-value
	Mean (SD)	**Mean (SD)**	
Pu SQ	31.54 (9.81)	24.33 (8.61)	0.000*
Ant SQ	26.72 (10.19)	21.46 (8.61)	0.002*

3.11 Association between NAFLD and BMI Subgroup

There was higher prevalence of obese subjects in NAFLD group (n=23; 35.94%) compared with the non-NAFLD group (n=10; 13.33%), p=0.002. Similarly, higher BMI value in the subjects with NAFLD (28.06 ± 5.51) as compared with those without NAFLD (25.16 ± 4.95), p = 0.001.

3.12 Association between NAFLD with underlying Medical Condition

In the NAFLD group, the prevalence of hyperlipidemia is 54.60% (35/64 patients); hypertension is 59.34% (38/64 patients); and for DM is 42.19% (27/64 patients). In the non-NAFLD group, the prevalence of hyperlipidemia is 49.33% (37/75 patients); hypertension is 57.33% (43/75 patients); and for DM is 34.67% (26/75 patients). For all three underlying medical conditions, there was no statistically significant difference between the two groups.

3.13 Association between NAFLD with Biochemical Values

There was a statistically significant lower HDL level in subjects with NAFLD compared with those without NAFLD. However, there were no statistical differences in the rest of the parameters of TG, TC, LDL, SUA, FPG and ALT between NAFLD and non NAFLD groups.

4.0 DISCUSSION

Our study observed a higher NAFLD prevalence rate of 46% in comparison with other Asian countries, where data for Asian populations had shown NAFLD prevalence of 21% in Shanghai (Fan et al., 2005), between 18% (Hamaguchi et al., 2005) and 31.7% (Omagari et al., 2009) in Japan and 13.5% in Thailand (Perera et al., 2008). Furthermore, according to Li J et al, in their systematic review and meta-analysis of NAFLD in Asia, showed the prevalence of NAFLD in Asia has increased from 25·28% between 1999 and 2005 to 33·90% between 2012 and 2017, with highest prevalence in Indonesia with 51.3% (Li et al., 2019). Our NAFLD prevalence is slightly lower than the study done by Magosso et al. (2010), where they detected 102 out of 180 (56.7%) fatty liver in their study, based on population of Northwestern Peninsular Malaysia (Magosso et al., 2010).

There was male preponderance in NAFLD in our study, which concurred with previous studies. Higher prevalence of NAFLD was found in male compared with female, where male individuals are more likely to distribute excess body fat in the intra-abdominal compartment (Schwimmer J.B., Mc Greal N., Deutsch R., Finegold M.J., & Lavine J.E., 2005). They hypothesised that the complications of obesity were attributable to accumulation of visceral adipose tissue in the mesentery and omentum. Another potential reason for a gender-based difference in fatty liver development is the influence of sex hormones, where sex hormones affect the distribution of both fat and muscle. Sex hormone binding globulin, produced in the liver, was proven to be strongly correlated with insulin sensitivity by Schwimmer et al. (2005).

Our study showed that the prevalence on DM, hyperlipidemia and HT in the NAFLD group was not significantly higher compared with the non-NAFLD group (N= 27, 29, 38 vs. 26, 38, 43 respectively, $p>0.05$). This was in contrast to the study done by Kirovski et al. (2010) whereby the reported rates of DM and HT were significantly higher in the NAFLD group (Kirovski et al., 2010). This may be contributed to relatively small sample size in our study. However, our study concurred with their observation on HDL level, where a lower HDL level was detected in the NAFLD group compared with non-NAFLD (mean 1.08 vs. 1.22, $p= 0.029$). Our study also concurred with previous study by Khammas et al. (2019) where they observed significantly higher prevalence of NAFLD in subjects with low HDL level (Khammas et al., 2019). While Suppiah S., Chow L.R-M., Sazali N.S., & Abu Hassan H. (2016) detected significantly higher LDL level in patients classified as having NAFLD, our study did not find similar observation. The discrepancies could be attributable to different sample populations between our studies, where Suppiah et al. (2016) concentrated on Metabolic X syndrome patients.

Gaba et al. (2012) in his study proved that there was an overall reduction in the CT liver attenuation value with increasing BMI (Gaba et al., 2012). The authors also showed that there was statistically significant increases in patients' BMIs in groups with greater degrees of steatosis. Kirovski et al. (2010) showed higher BMI classes in patients with NAFLD compared with the non-NAFLD (Kirovski et al., 2010). The results of our study were consistent with these literature reviews, showing that the average CT attenuation value of the liver density was lower in the group of obese patients compared with the control group. We also observed that the NAFLD group had a higher BMI compared with the non-NAFLD group.

Our study observed that the mean and distribution of average CT liver attenuation value were lower in the group of patients with increased Pu SQ of ≥ 21.4mm. This was consistent with the study by Kirovski et al. (2010) where they found that the Pu SQ was significantly higher in patients with ultrasound-diagnosed NAFLD with mean 21.4 ± 11.7 mm versus the control (mean 15.7 ± 9.2 mm), (p=0.001). In addition, his results also showed that the Pu SQ was significantly correlated with the BMI (r=0.65) (Kirovski et al., 2010).

Furthermore, we also demonstrated that the distribution of average CT liver attenuation value was lower with increased Ant SQ of ≥ 24mm. This finding supported the findings by Gaba et al. (2012) where they proposed that the combination of a BMI ≥32.0 kg/m2 and an Ant SQ ≥2.4 cm had 40% (27/67) sensitivity and 90% (68/76) specificity for the identification of hepatic steatosis for all patients (positive predictive value =27/35, 77%; negative predictive value = 68/108, 63%) (Gaba et al., 2012).

We also observed that the mean of the Ant SQ was higher in the NAFLD group (mean 26.72 +/-10.19) and Pu SQ (mean 31.54 +/- 9.81) compared with the non- NAFLD group (mean 21.46 +/-8.61; and mean 24.33 +/- 8.61 respectively, p<0.005). This was consistent with Gaba et al (2012) study, which showed that anterior subcutaneous fat thickness had a moderate correlation with the presence of liver steatosis (r=0.30, P < 0.001) (Gaba et al., 2012). In addition, our study showed that there was inverse correlation between CT Liver attenuation Value with the Ant SQ, Pu SQ and BMI, although Pearson Coefficient showed weak correlations with r = - 0.286, r =-0.297, r = -0.328 respectively.

5.0 CONCLUSION

In conclusion, our study showed that NAFLD had increasing incidence with increasing BMI, increasing anterior subcutaneous wall and paraumbilical subcutaneous wall thickness, as well as lower HDL level. We also concluded that there was an inverse correlation between the average CT liver attenuation value, with the BMI classes and anthropometric measurements whereby there was decreasing average CT liver attenuation value with increasing BMI and anthropometric measurements. There was also significant difference in BMI obese group, Ant SQ and Pu SQ, and HDL mean level between the NAFLD and non-NAFLD groups.

REFERENCES

Anand S.S., Tarnopolsky M.A., Rashid S., Schulze K.M., Desai D., Mente A., … & Sharma A.M. (2011). Adipocyte hypertrophy, fatty liver and metabolic risk factors in South Asians: the Molecular Study of Health and Risk in Ethnic Groups (mol-SHARE). *PLoS One, 6*(7), e22112. doi: 10.1371/journal.pone.0022112. Epub 2011 Jul 28

Fan J.G., Zhu J., Li X.J., Chen L., Li L., Dai F., Li F., & Chen S.Y. (2005). Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. *Journal of hepatology, 43*(3), 508- 14.

Gaba R.C., Knuttinen M.G., Brodsky T.R., Palestrant S., Omene B.O., Owens C.A., & Bui J.T. (2012). Hepatic steatosis: correlations of body mass index, CT fat measurements, and liver density with biopsy results. *Diagnostic and Interventional Radiology*, *18*(3), 282-7.

Hamaguchi M., Kojima T., Takeda N., Nakagawa T., Taniguchi H., Fujii K., … & Ida K. (2005). The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Annals of Internal Medicine*, *143*(10), 722-8.

Khammas A.S.A., Hassan H.A., Salih S.Q.M., Kadir H., Ibrahim R.M., Nasir N.N.M., & Mahmud R. (2019). Prevalence and risk factors of sonographically detected non-alcoholic fatty liver disease in a screening centre in Klang Valley, Malaysia: an observational cross-sectional study. *Porto Biomed J*, 4(2)e31.

Kirovski G., Schacherer D., Wobser H., Huber H., Niessen C., Beer C., … & Hellerbrand C. (2010). Prevalence of ultrasound- diagnosed non- alcoholic fatty liver disease in a hospital cohort and its association with anthropometric, biochemical and sonographic characteristics. *International journal of clinical and experimental medicine*, *3*(3), 202-10.

Li J., Zou B., Yeo Y.H., Feng Y., Xie X., Lee D.H., … & Nguyen M.H. (2019). Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*, *4*, 389–98.

Magosso E., Ansari M.A., Gopalan Y., Abu Bakar M.R., Karim Khan N.A., Wong J.W., … & Nesaretnam K. (2010). Prevalence of non-alcoholic fatty liver in a hypercholesterolemic population of northwestern peninsular Malaysia. *The Southeast Asian journal of tropical medicine and public health*, *41*(4), 936-42.

NHMS. (2011). *National Health and Morbidity Survey*. NHMS_2011_FACT_SHEET.pdf.

Omagari K., Morikawa S., Nagaoka S., Sadakane Y., Sato M., Hamasaki M., … & Sera K. (2009). Predictive factors for the development or regression of fatty liver in Japanese adults. *Journal of clinical biochemistry and nutrition*, *45*(1), 56-67.

Perera S., Lohsoonthorn V., Jiamjarasrangsi W., Lertmaharit S., & Williams M.A. (2008). Association between elevated liver enzymes and metabolic syndrome among Thai adults. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews.*, *2*(3), 171-8.

Schwimmer J.B., Mc Greal N., Deutsch R., Finegold M.J., & Lavine J.E. (2005). Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents. *Pediatrics*, *115*(5), e561-5.

Suppiah S., Chow L.R-M., Sazali N.S., & Abu Hassan H. (2016). Non-Alcoholic Fatty Liver Disease in Metabolic Syndrome Patients in Serdang Hospital: Quantification by Contrast-Enhanced Computed Tomography. *Malaysian Journal of Medicine and Health Sciences.*, *12*(1), 9-18.

WHO Expert Consultation. (2004). Appropriate body mass index for Asian populations and its implication for policy and intervention strategies. *Lancet*, *363*, 157-67.