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Original Article

Sex-specific Cutoff Values of Visceral Fat Area for Lean vs. Overweight/Obese Nonalcoholic Fatty Liver Disease in Asians

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Abstract

Background and Aims: Visceral obesity is a risk factor for nonalcoholic fatty liver disease (NAFLD). We investigated sex-specific optimal cutoff values for visceral fat area (VFA) associated with lean and overweight/obese NAFLD in an Asian population. ***Methods:*** This retrospective study included 678 potential living liver donors (mean age, 30.8±9.4 years; 434 men and 244 women) who had undergone abdominal computed tomography (CT) imaging and liver biopsy between November 2016 and October 2017. VFA was measured using single-slice abdominal CT. NAFLD was evaluated by liver biopsy (≥5% hepatic steatosis). Receiver operating characteristic curve analysis was used to determine cutoff values for VFA associated with lean (body mass index [BMI] <23 kg/m^2) and overweight/obese (BMI ≥23 kg/m^2) NAFLD. ***Results:*** Area under the curve (AUC) values with 95% confidence intervals (CI) for VFA were 0.82 (95% CI, 0.75–0.88) for lean and 0.74 (95% CI, 0.69–0.79) for overweight/obese men with NAFLD. The AUC values were 0.67 (95% CI, 0.58–0.75) for lean and 0.71 (95% CI, 0.62–0.80) for overweight/obese women with NAFLD. The cutoff values for VFA associated with lean NAFLD were 50.2 cm^2 in men and 40.5 cm^2 in women. The optimal cutoff values for VFA associated with overweight/obese NAFLD were 100.6 cm^2 in men and 68.0 cm^2 in women. ***Conclusions:*** Sex-specific cutoff values for VFA may be useful for identifying subjects at risk of lean and overweight/obese NAFLD.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CT, computed tomography; HDL, high-density lipoprotein; HS, hepatic steatosis; MR, magnetic resonance; NAFLD, nonalcoholic fatty liver disease; ROC, receiver operating characteristic; SD, standard deviation; US, ultrasound; VFA, visceral fat area.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major etiology of chronic liver disease worldwide.[1] The diagnosis of NAFLD is confirmed by the presence of ≥5% hepatic steatosis (HS) either on imaging or histology in the absence of secondary causes for hepatic fat accumulation (e.g., excessive alcohol consumption, use of steatogenic medications, or hereditary disorders).[2] Although NAFLD is associated with obesity and has been reliably established as a hepatic manifestation of the metabolic syndrome, it can also occur in lean patients, i.e., those having body mass indices (BMIs) of <23 kg/m^2 in Asians or <25 kg/m^2 in non-Asians.[3,4] Recent studies have indicated that visceral obesity may have a more important role in development of the metabolic syndrome and NAFLD than generalized obesity.[5,6]

While the diagnosis of NAFLD can be determined by imaging, including ultrasonography, the controlled attenuation parameter of transient elastography, computed tomography (CT), and magnetic resonance (MR) spectroscopy or proton density fat fraction, histological analysis of liver biopsies is regarded as the gold standard.[7] For evaluation of visceral adiposity, CT imaging is considered the gold standard.[8] Although many studies have identified values for visceral adiposity associated with the metabolic syndrome,[9–14] few have focused on NAFLD.[15] Moreover, appropriate cutoff values for visceral fat area (VFA) stratified by sex and BMI for NAFLD have not been identified in studies using gold-standard methods. We aimed to identify sex-specific optimal cutoff values for VFA, measured by CT imaging, and associated with lean and overweight/obese NAFLD assessed by liver biopsy, in an Asian population.

Methods

The study was approved by the institutional review board of our institution. The requirement for written informed consent was waived because the analysis was retrospective.

Study population

Our institution's databases were retrospectively searched to identify living liver donor candidates who had undergone an abdominal CT imaging examination and ultrasound

Table 1. Participant characteristics

	Total (*n*=678)	Male (*n*=434)	Female (*n*=244)	*p*-value
Age, y	30.8±9.4	29.5±9.0	33.3±9.6	<0.001
Body mass index, kg/m^2	23.6±3.1	24.0±2.9	22.9±3.5	<0.001
AST, IU/L	22.3±23.1	23.9±26.7	19.6±14.2	0.021
ALT, IU/L	21.9±29.5	25.3±34.6	16.0±15.5	<0.001
Total cholesterol, mg/dL	177.1±35.3	177.7±35.2	175.8±35.4	0.498
Triglyceride, mg/dL	109.3 ±74.8	122.9±80.9	86.2±56.3	<0.001
HDL, mg/dL	56.6±14.1	53.2±12.6	62.4±14.5	<0.001
Visceral fat area, cm^2	68.3±45.9	78.3±49.1	50.5±32.7	<0.001

Data are mean±standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein.

(US)-guided percutaneous liver biopsy as part of a routine predonation evaluation between November 2016 and October 2017. The medical evaluation process consisted of three phases. Phase 1 comprised a clinical examination, review of the past medical history, and laboratory tests, including viral serology. Subjects who consumed more than 20 g of alcohol per day or used drugs regularly including herbal medications were considered inappropriate for liver donation. Donor candidates who had diabetes mellitus, hypertension, or any other significant medical diseases were excluded from right liver donation. Subjects with serologic evidence of hepatitis B or hepatitis C were excluded from liver donation. Phase 2 included liver CT to evaluate vascular anatomy, hepatic volume, and steatosis. Phase 3 consisted of MR cholangiography and indocyanine green retention tests.

CT image acquisition

CT scans were performed with a 128-slice (Definition AS+ or Edge, Siemens, Erlangen, Germany) multidetector-row CT scanner. Unenhanced CT scans were obtained, followed by biphasic contrast-enhanced CT (hepatic arterial and portal venous phases) after administration of 150 mL of iopromide (Ultravist 370, Bayer Schering Pharma, Berlin, Germany) for anatomical mapping of the hepatic vasculature and CT volumetry. The scanning and reconstruction parameters were beam collimation of 128 slices by 0.6 mm, spiral pitch of 1, gantry rotation time of 0.5 s, tube voltage of 100 or 120 kVp, tube current of 120–200 mAs with automatic exposure control (Care Dose 4D, Siemens), and section thickness and interval of 5 mm.

Assessment of abdominal fat parameters

A single axial CT image at the level of the inferior endplate of the L3 lumbar vertebra was processed for each patient. Abdominal CT image analysis was performed with a fully convolutional network-based automatic segmentation technique using a deep learning system.[16] Assessment of body composition was conducted using artificial intelligence software (AIDU, iAID Inc., Seoul, Republic of Korea).[16] CT images were automatically segmented to generate boundaries, with measurement of abdominal fat. The VFA (cm^2) was demarcated using fat-tissue thresholds (−190 to −30 Hounsfield units).

Liver biopsy

As part of the living liver donor evaluation, US-guided percutaneous biopsy of the right hepatic lobe was performed using an 18-gauge needle (Stericut 18G coaxial, TSK Laboratory, Tochigi, Japan). Two or more biopsy specimens, each approximately 1.5 cm in length, were obtained and stained with hematoxylin and eosin. The degree of HS was assessed as the percentage of liver parenchyma replaced by steatotic droplets. NAFLD was defined as the presence of ≥5% HS.[2]

Data collection

Demographic data (age and sex), anthropometric measurements (body weight and height), and laboratory parameters [serum AST, ALT, total cholesterol, triglycerides, high-density lipoprotein (HDL)] were collected. BMI (kg/m^2) status was determined using ethnicity-specific cutoff values of <23 kg/m^2 for lean, 23–24.9 kg/m^2 for overweight, and ≥25 kg/m^2 for obese.[17]

Statistical analysis

Descriptive values are reported as mean±standard deviation (SD). Differences between male and female subjects were evaluated with two-sample *t*-tests. Subject characteristics of were analyzed according to lean vs. overweight/obese status and the presence or absence of NAFLD using one-way analysis of variance, followed by *post hoc* analysis using the Bonferroni method. Receiver operating characteristic (ROC) curve analysis was used to assess the accuracy of identifying the presence of NAFLD in lean and overweight/obese subjects. Accuracy was measured by area under the curve (AUC) with 95% confidence intervals (CIs). Sex-specific cutoff values for VFA were chosen to maximize the sum of the sensitivity and specificity of Youden's index. At optimal cutoff values, sensitivity and specificity with 95% CIs were determined. Statistical significance was set at a *p*-value of <0.05. Statistical analysis was performed with SPSS 23.0 (IBM Corp., Armonk, NY, USA) and MedCalc 16.2.1 (MedCalc Software, Ostend, Belgium).

Results

A total of 678 subjects (30.8±9.4 years of age, 434 men, and 244 women) were included in the analysis. Their baseline characteristics are summarized in Table 1. The BMI, serum AST, ALT, and triglycerides, and VFA were higher in men and age and serum HDL were higher in women.

The study cohort was divided into subgroups by BMI and

Table 2. Features of study subjects stratified by BMI and NAFLD status and subdivided by sex

	Lean without NAFLD	Lean NAFLD	Overweight/obese without NAFLD	Overweight/obese NAFLD	*p*-value
Male (*n*=434)					
n	99	59	147	129	
Age, y	26.7±7.8	31.3±8.2[a]	28.2±8.4	32.2±10.1[a,c]	<0.001
Body mass index, kg/m^2	21.1±1.4	21.6±1.3	25.3±2.1[a,b]	25.8±2.6[a,b]	<0.001
AST, IU/L	22.1±13.2	24.4±18.0	21.2±9.8	28.1±44.7	0.161
ALT, IU/L	17.9±12.8	28.2±23.2	22.0±14.2	33.4±57.6[a,c]	0.004
Total cholesterol, mg/dL	168.4±29.9	187.2±37.7[a]	175.2±35.4	183.5±35.8[a]	0.001
Triglyceride, mg/dL	98.8±70.8	132.9±98.8	116.8±66.1	146.5±87.9[a,c]	<0.001
HDL, mg/dL	58.2±13.3	52.1±11.5[a]	53.7±13.1[a]	48.7±10.4[a,c]	<0.001
Visceral fat area, cm^2	41.4±27.7	80.5±35.6[a]	71.9±44.1[a]	113.0±49.6[a,b,c]	<0.001
Female (*n*=244)					
n	114	21	69	40	
Age, y	33.6±8.4	34.9±8.7	31.1±9.8	35.4±12.3	0.109
Body mass index, kg/m^2	20.5±1.6	20.7±1.4	25.6±2.5[a,b]	26.5±3.1[a,b]	<0.001
AST, IU/L	19.6±16.0	17.7±3.1	19.8±15.4	20.5±9.7	0.909
ALT, IU/L	14.1±14.2	14.7±5.5	17.7±17.9	18.9±17.9	0.258
Total cholesterol, mg/dL	174.2±30.7	179.2±40.2	171.8±40.1	186.3±36.1	0.185
Triglyceride, mg/dL	77.7±58.7	75.9±47.3	87.2±48.8	115.3±56.8[a,b]	0.004
HDL, mg/dL	65.8±14.0	66.1±17.0	60.2±14.4	54.2±10.9[a,b]	<0.001
Visceral fat area, cm^2	32.1±19.0	47.1±27.2[a]	61.1±28.5[a]	86.8±35.9[a,b,c]	<0.001

Data are mean±standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease. [a]p<0.05 by *post hoc* analyses vs. lean without NAFLD. [b]p<0.05 by *post hoc* analyses vs. lean NAFLD. [c]p<0.05 by *post hoc* analysis vs. overweight/obese without NAFLD.

NAFLD as lean without NAFLD, lean with NAFLD, overweight/obese without NAFLD, and overweight/obese with NAFLD. The subgroup characteristics subdivided by sex are shown in Table 2. In men, subgroup differences in age, BMI, serum ALT, total cholesterol, triglyceride, and HDL levels, and VFA were significant (p≤0.004). In women, subgroup differences in BMI, serum triglyceride, and HDL levels, and VFA were significant (p≤0.004). In both lean and overweight/obese subjects, VFA tended to be higher in those with NAFLD than in those without NAFLD, and *post hoc* analysis showed that the VFA in lean subjects with NAFLD and overweight/obese without NAFLD of either sex were not significant (men, p>0.999 and women, p=0.189).

Table 3 and Figure 1 report the AUC values of VFA for identifying lean and overweight/obese NAFLD. NAFLD was found in 37.3% lean and 46.7% of overweight/obese men and 15.6% of lean and 36.7% of overweight/obese women. The AUCs were 0.82 (95% CI, 0.75–0.88) for lean and 0.74 (95% CI, 0.69–0.79) for overweight/obese men and 0.67 (95% CI, 0.58–0.75) for lean and 0.71 (95% CI, 0.62–0.80) for overweight/obese women. The optimal cutoff values for VFA for lean and overweight/obese NAFLD were 50.2 cm^2 and 100.6 cm^2, respectively, in men and 40.5 cm^2 and 68.0 cm^2, respectively, in women. In men, the sensitivity and specificity at the optimal VFA cutoffs were 81.4% (95% CI, 69.1–90.3%) and 71.7% (95% CI, 61.8–80.3%), respectively, for lean, and 61.2% (95% CI, 52.3–69.7%) and 76.2% (95% CI, 68.5–82.8%), respectively, for overweight/obese NAFLD. In women, the sensitivity and specificity at the optimal VFA cutoffs were 57.1% (95% CI, 34.0–78.2%) and 81.6% (95% CI, 73.2–88.2%), respectively, for lean NAFLD and 70.0% (95% CI, 53.5%–83.4%) and 69.6% (95% CI, 57.3–80.1%), respectively, for overweight/obese NAFLD.

Table 3. Optimal cutoff values for VFA for identifying lean and overweight/obese NAFLD subdivided by sex

	Lean NAFLD		Overweight/obese NAFLD	
	Male	Female	Male	Female
AUC (95% CI)	0.82 (0.75–0.88)	0.67 (0.58–0.75)	0.74 (0.69–0.79)	0.71 (0.62–0.80)
Optimal VFA cutoff value, cm^2	50.2	40.5	100.6	68.0
Sensitivity (95% CI), %	81.4 (69.1–90.3)	57.1 (34.0–78.2)	61.2 (52.3–69.7)	70.0 (53.5–83.4)
Specificity (95% CI), %	71.7 (61.8–80.3)	81.6 (73.2–88.2)	76.2 (68.5–82.8)	69.6 (57.3–80.1)

Optimal VFA cutoff values were defined by the maximal sum of sensitivity and specificity. AUC, area under the curve; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; VFA, visceral fat area.

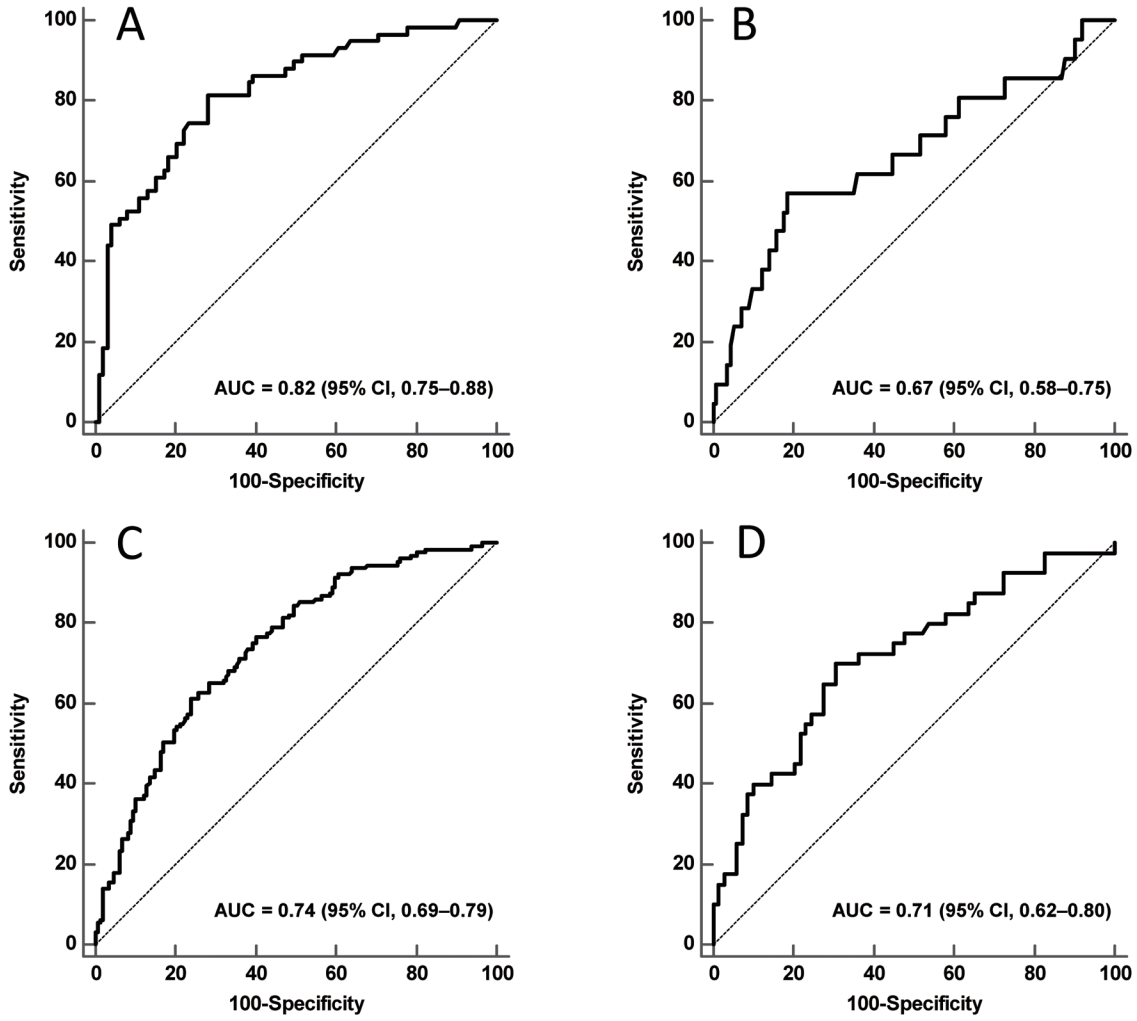

Fig. 1. Receiver operating characteristic curves for visceral fat area to identify (A) lean nonalcoholic fatty liver disease (NAFLD) in men, (B) in lean women, (C) in overweight/obese men, and (D) overweight/obese in women.

Discussion

The VFA tended to be higher in subjects with NAFLD than in those without NAFLD in both lean and overweight/obese potential living liver donors who underwent abdominal CT imaging and liver biopsy. We also identified optimal VFA cutoff values for identifying the presence of NAFLD stratified by sex and BMI status.

Although obesity is generally related to NAFLD, a considerable number of patients with NAFLD are nonobese or even lean, and a substantial proportion of overweight or obese individuals do not develop NAFLD.[3] The development of NAFLD may be related to adipose tissue distribution, and visceral adipose tissue is widely accepted as a risk factor for NAFLD independent of generalized obesity.[18] Our study also demonstrated that the mean VFA was higher in subjects with NAFLD than in those without NAFLD in both lean and overweight/obese groups. Visceral fat has higher lipolytic activity, and directly releases free fatty acids into the liver via the portal circulation, which may substantially contribute to HS.[19] Increased visceral fat results in increased production of cytokines and adipokines, leading to disease progression in NAFLD.[3] In addition, our study showed that the VFA was not significantly different between lean subjects with NAFLD and overweight/obese subjects without NAFLD in either sex, indicating that visceral fat accumulation was as high in lean subjects with NAFLD as it was in overweight/obese individuals, which is consistent with a previous study in a Chinese population that used MR imaging to detect HS and measure visceral fat.[20]

Many studies have investigated the optimal cutoffs for visceral fat indices when screening for the metabolic syndrome,[9–14] but to the best of our knowledge, there has been only one study that established optimal VFA cutoffs for NAFLD.[15] In a study by Yoon *et al*.[15] in a Korean population, the optimal VFA cutoffs at the L4-L5 level for detecting NAFLD, measured by CT imaging, were 132 cm^2 in men and 119 cm^2 in women. In that study, the liver attenuation index derived from the difference between mean hepatic and splenic attenuation on unenhanced CT imaging was used in the diagnosis of NAFLD.[15] Unlike that study,[15] we generated sex-specific cutoff values for CT-measured VFA at the L3 level to separate metabolically normal Koreans from those with lean and overweight/obese NAFLD, as assessed by liver biopsy (i.e., the gold standard for an NAFLD diagnosis). We propose VFA cutoffs of 50.2 cm^2 in men and 40.5 cm^2 in women to identify those at risk of lean NAFLD, and 100.6 cm^2 in men and 68.0 cm^2 in women to identify those at risk

of overweight/obese NAFLD. The values may be useful for identifying patients in whom visceral obesity places them at increased risk for lean or overweight/obese NAFLD. In addition, they may be used as therapeutic target values for visceral fat reduction to resolve NAFLD.

The study has several limitations. First, it was a preliminary retrospective study conducted at a single center, and the number of enrolled subjects was not large. Prospective multicenter, studies with more participants are needed to confirm our results. Second, the study included potential living liver donors who had undergone liver biopsy as part of a predonation workup. The inclusion criteria were implemented to assess NAFLD and VFA using gold standard diagnostic methods, but that may have resulted in selection bias. Also, noninvasive evaluation of HS by transient elastography was not performed in this study. In addition, the enrolled subjects were relatively young adults capable of donating their livers. Therefore, it is unclear whether they are representative of the general population. Third, we included only Korean subjects, which may have limited the generalizability of our findings to other ethnicities. So, our findings need to be validated by trials in a broader population. Fourth, the prevalence of NAFLD in lean men (37.3%) was much higher than previously reported,[4,21,22] so it may have led to the better performance of AUC in lean men with NAFLD than in the other groups.

In conclusion, the cutoff values of CT-measured VFA for identifying NAFLD were influenced by sex and BMI. Sex-specific cutoff values for VFA may be useful for identifying lean and overweight/obese individuals at risk of NAFLD.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to the study concept and design, analysis and interpretation of data, drafting of the manuscript, material support, and study supervision (SL), acquisition of data (JL), critical revision of the manuscript for important intellectual content and administrative, technical support (KWK).

Data sharing statement

The data used to support the findings of this study are available from the corresponding author upon request.

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