Post-print: A Retrospective Cohort Study on Chinese Visceral Adiposity Index and Risk of Fatty Liver Disease

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Abstract

Background Obesity is an important risk factor for the development of fatty liver disease; however, current diagnostic indicators for obesity cannot effectively reflect the role of adipose tissue distribution in the pathogenesis of fatty liver disease. Objective To evaluate the association between baseline visceral adiposity index (VAI) and Chinese visceral adiposity index (CVAI) and the risk of incident fatty liver disease. Methods This was a retrospective cohort study that included 17,086 adult health examination participants from the Health Management Center of Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing University Medical School, between February 2018 and November 2021 as study subjects. Basic information, general physical examination data, laboratory indicators, and instrumental examination results were collected by reviewing health examination records through the electronic information system of the Health Management Center. Incident fatty liver disease was determined based on follow-up abdominal ultrasound and CT results. Follow-up was conducted until December 2022. The follow-up endpoint was defined as the period from no fatty liver disease at baseline to the first occurrence of fatty liver disease or the last follow-up time. Participants were divided into two groups according to whether they developed fatty liver disease during follow-up, and baseline VAI and CVAI were compared between the two groups. Based on the quartile levels of baseline VAI and CVAI, the population was each divided into four groups, and the incidence of fatty liver disease was compared among the four groups. Cox regression analysis was used to evaluate the association between VAI, CVAI and incident fatty liver disease, and receiver operating characteristic (ROC) curves were used to assess the predictive value of VAI and CVAI for fatty liver disease incidence. Delong's test was used to compare the difference in AUC between VAI and CVAI. Results The mean age of the included participants was $(44.3\$\pm13.2)years, meanBMIwas(23.2\pm2.6)kg/m^{\{2\}}, andmeanfollow-updurationwas(2.7\pm1.1)years.Bytheendoffollow-$ trend=1,034.9 and 1,334.8, P<0.001). Multivariate Cox regression analysis

revealed that the risk of developing fatty liver disease in the VAI-Q4 and CVAI-Q4 groups was 2.579 times (95%CI=2.088-3.186) and 3.375 times (95%CI=2.488-4.576) that of the VAI-Q1 group, respectively. ROC curves showed that the area under the curve for CVAI in predicting fatty liver disease was greater than that for VAI (0.737 vs. 0.708, P<0.001). Stratified analysis showed that the CVAI-Q4 group was associated with incident fatty liver disease across different sex, age, and BMI subgroups (P<0.001). Conclusion Baseline CVAI is significantly associated with incident fatty liver disease, and CVAI demonstrates superior predictive ability for fatty liver disease incidence compared to VAI.

Full Text

A Retrospective Cohort Study of the Chinese Visceral Adiposity Index and Risk of Fatty Liver

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Abstract

Background: Obesity is an important risk factor for the development of fatty liver. However, current diagnostic indices for obesity cannot effectively reflect the role of adipose tissue distribution in fatty liver pathogenesis. **Objective:** To evaluate the association between baseline visceral adiposity index (VAI) and Chinese visceral adiposity index (CVAI) with the risk of incident fatty liver.

Methods: This retrospective cohort study included 17,086 adults undergoing physical examination at the Health Management Center of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, between February 2018 and November 2021. Health examination records were retrieved from the center's electronic information system to collect baseline characteristics, physical examination findings, laboratory measurements, and imaging results. Incident fatty liver was determined based on follow-up abdominal ultrasound and CT findings, with follow-up continuing through December 2022. The follow-up period was defined as the interval from baseline (absence of fatty liver) to the first occurrence of fatty liver or the final follow-up date. Participants were divided into two groups according to whether they developed fatty liver during follow-up, and baseline VAI and CVAI were compared between groups. The

population was further stratified into four groups based on quartiles of baseline VAI and CVAI to compare fatty liver incidence across groups. Cox regression analysis was used to evaluate the association between VAI/CVAI and fatty liver incidence. Receiver operating characteristic (ROC) curves were constructed to assess the predictive value of VAI and CVAI for fatty liver development, and Delong's test was used to compare differences in area under the curve (AUC) between the two indices.

Results: The mean age of participants was $(44.3\$\pm13.2)years, meanBMIwas(23.2\pm2.6)kg/m^{\{2\},andmeanfollou$ trend = 1,034.9 and 1,334.8, respectively, both P<0.001). Multivariate Cox regression analysis showed that the risk of fatty liver in the VAI-Q4 and CVAI-Q4 groups was 2.579 times (95%CI=2.088–3.186) and 3.375 times (95%CI=2.488–4.576) that of the VAI-Q1 group, respectively. ROC curve analysis demonstrated that the AUC of CVAI for predicting fatty liver was greater than that of VAI (0.737 vs. 0.708, P<0.001). Stratified analysis showed that the CVAI-Q4 group was associated with fatty liver incidence across different sex, age, and BMI subgroups (P<0.001).

Conclusion: Baseline CVAI is significantly associated with incident fatty liver, and its predictive ability for fatty liver development is superior to that of VAI. These findings indicate that CVAI has good predictive value for fatty liver occurrence in Chinese populations and may be useful for early identification of high-risk individuals.

Keywords: Fatty liver; Obesity; Chinese visceral adiposity index; Visceral adiposity index; Risk factors

Introduction

Fatty liver disease, characterized by abnormal lipid deposition in the liver, has become the most common chronic liver disease worldwide. It not only increases the risk of cirrhosis and hepatocellular carcinoma but also contributes to the development of diabetes, cardiovascular disease, and chronic kidney disease, imposing a substantial economic burden on society. Obesity has long been recognized as a major risk factor for fatty liver, and the global prevalence of fatty liver has been rising in parallel with the obesity epidemic. The situation is particularly concerning in China, where a recent real-world cross-sectional study of 15.8 million adults found that fatty liver has become the most common complication among obese individuals, with a prevalence as high as 81.8%.

Accumulating evidence demonstrates that visceral fat content is closely associated with hepatic steatosis, inflammatory responses, and fibrosis severity. However, despite the well-established link between obesity and fatty liver, current diagnostic criteria for obesity remain based solely on body mass index (BMI), which cannot accurately reflect the role of adipose tissue distribution in disease severity. While computed tomography (CT) and magnetic resonance imaging

(MRI) enable precise assessment of fat distribution, their high cost, time requirements, and radiation exposure limit routine clinical application. Consequently, researchers have developed various indices to evaluate fat distribution, including the visceral adiposity index (VAI). Nevertheless, significant differences in fat distribution across races, sexes, and age groups have led some investigators to conclude that VAI may not adequately capture adipose tissue distribution patterns in Chinese populations.

In 2016, Chinese researchers developed the Chinese visceral adiposity index (CVAI) based on population-specific characteristics of fat distribution in Asian populations. CVAI has since been shown to correlate significantly with cardiovascular disease, type 2 diabetes, metabolic syndrome, and fatty liver disease. However, most existing studies are cross-sectional, and longitudinal research examining CVAI's predictive value for incident fatty liver remains limited. Therefore, this large-scale retrospective cohort study of a physical examination population aims to clarify the relationship between baseline CVAI and fatty liver development, providing a basis for early identification of high-risk individuals.

1.1 Study Population

This retrospective cohort study included 17,086 adults undergoing physical examination at the Health Management Center of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, between February 2018 and November 2021. Inclusion criteria were: (1) age $\geq$ 18 years; (2) at least two abdominal ultrasound or CT examinations with an interval of $\geq$ 360 days. Exclusion criteria were: (1) presence of fatty liver at baseline; (2) history of viral hepatitis, autoimmune liver disease, or cirrhosis; (3) acute or chronic hepatic or renal insufficiency, infectious diseases, or malignant tumors at baseline; (4) missing clinical data including fasting blood glucose, alanine aminotransferase, aspartate aminotransferase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol. This study was approved by the Ethics Committee (approval number: 2022-444-01).

1.2 Data Collection and Follow-up

1.2.1 Data Collection: Health examination records were retrieved from the center's electronic information system to collect baseline characteristics, physical examination findings, laboratory measurements, and imaging results. Physical examinations included height, body weight, waist circumference, systolic blood pressure, and diastolic blood pressure. Imaging studies included ultrasound and CT examinations. Laboratory measurements included fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). BMI, VAI, and CVAI were calculated using the following formulas: (1) BMI = weight (kg) / height^2 (m^2); (2) VAI (male) = waist circumference (cm) / (39.68 + 1.88 $\times$ BMI) $\times$ TG (mmol/L) / 1.03 $\times$ 1.31 / HDL-C (mmol/L), VAI (female) = waist circumference / (36.58 + 1.89 $\times$ BMI) $\times$ TG

/ 0.81 × 1.52 / HDL-C; (3) CVAI (male) = -267.93 + 0.68 × age + 0.03 × BMI + 4.00 × waist circumference + 22.00 × $\log_{10}$(TG) - 16.32 × HDL-C, CVAI (female) = -187.32 + 1.71 × age + 4.23 × BMI + 1.12 × waist circumference + 39.76 × $\log_{10}$(TG) - 11.66 × HDL-C.

1.2.2 Grouping and Follow-up: Incident fatty liver was determined based on follow-up abdominal ultrasound and CT results. All ultrasound examinations were performed by experienced sonographers ($ $5 years of experience) at our hospital, and fatty liver was diagnosed when ultrasound reports described features recommended by guidelines (if ultrasound results were inconsistent with imaging reports within the previous 3 months, a sonographer review was requested). Follow-up continued through December 2022, with the follow-up period defined as the interval from baseline (absence of fatty liver) to the first occurrence of fatty liver or the final follow-up date.

1.3 Statistical Analysis

Statistical analysis was performed using SPSS 26.0 and R 4.2.3 software. Continuous variables with normal distribution were expressed as mean ± standard deviation and compared between groups using t-tests. Non-normally distributed continuous variables were expressed as median (P_{25}, P_{75}) and compared using Mann-Whitney U tests. Categorical data were expressed as frequency (percentage) and compared using ^{2} tests. Linear trends between grouping variables and fatty liver incidence were assessed using Mantel-Haenszel ^{2} tests. Cox proportional hazards models were used to evaluate the association between VAI/CVAI and fatty liver incidence. Kaplan-Meier survival curves were constructed, and differences were compared using Log-rank tests. Receiver operating characteristic (ROC) curves were used to assess the predictive value of VAI and CVAI for fatty liver development, and Delong's test was used to compare AUC differences between the two indices. A two-sided P<0.05 was considered statistically significant.

Results

2.1 Baseline Characteristics of Participants

Among the 17,086 participants, 9,461 (55.4%) were male and 7,625 (44.6%) were female. Baseline age ranged from 18 to 75 years, with a mean age of $(44.3\$\pm13.2)years.BaselineBMIrangedfrom18.0to36.8kg/m^{\{2\},withameanBMIof(23.2\pm2.6)kg/m}\{2\}.Follow-updurationrangedfrom1.0to4.7years,withameanfollow-upof(2.7\pm\$1.1)$ years. By the end of follow-up, 2,523 participants (14.8%) had developed fatty liver.

2.2 Comparison of Baseline Clinical Data

Compared with the non-fatty liver group, participants who developed fatty liver had significantly higher baseline age, BMI, waist circumference, systolic blood

pressure, diastolic blood pressure, ALT, AST, FBG, HbA1c, TG, TC, and LDL-C, and significantly lower HDL-C (all P<0.001). Additionally, both VAI and CVAI were significantly higher in the fatty liver group than in the non-fatty liver group (P<0.001, Table 1).

2.3 Association Between VAI, CVAI and Fatty Liver Incidence

Based on VAI quartiles, participants were divided into four groups: Q1 (VAI ≤ 0.64, n=4,317), Q2 (0.64<VAI ≤ 0.96, n=4,243), Q3 (0.96<VAI ≤ 1.51, n=4,258), and Q4 (VAI ≥ 1.51, n=4,268), with fatty liver incidence rates of 4.8% (208/4,317), 9.2% (390/4,243), 16.9% (719/4,258), and 28.3% (1,206/4,268), respectively. Similarly, based on CVAI quartiles, participants were divided into Q1 (CVAI ≤ 30.70, n=4,271), Q2 (30.70<CVAI ≤ 63.89, n=4,270), Q3 (63.89<CVAI ≤ 92.95, n=4,274), and Q4 (CVAI ≥ 92.95, n=4,271), with fatty liver incidence rates of 2.6% (112/4,271), 9.3% (398/4,270), 17.7% (758/4,274), and 29.4% (1,255/4,271), respectively. Trend analysis showed that fatty liver incidence increased significantly with increasing baseline VAI and CVAI levels (^{2} trend = 1,034.9 and 1,334.8, respectively, both P<0.001).

Univariate Cox regression analysis, with fatty liver incidence as the dependent variable (yes=1, no=0), revealed that the VAI-Q4 and CVAI-Q4 groups had 5.734-fold (95%CI=4.949–6.643) and 11.241-fold (95%CI=9.263–13.642) higher risks of fatty liver compared to the VAI-Q1 group, respectively. After further adjustment for sex, age, BMI, waist circumference, systolic blood pressure, ALT, AST, TG, TC, HDL-C, and LDL-C in multivariate Cox regression analysis, both VAI and CVAI remained independently associated with fatty liver risk. The VAI-Q4 and CVAI-Q4 groups had 2.579-fold (95%CI=2.088–3.186) and 3.375-fold (95%CI=2.488–4.576) higher risks of fatty liver compared to the VAI-Q1 group, respectively (Table 2).

2.4 Predictive Value of VAI and CVAI for Fatty Liver Incidence

ROC curve analysis showed that the AUCs for VAI and CVAI in predicting fatty liver were 0.708 (95%CI=0.697–0.718) and 0.737 (95%CI=0.728–0.747), respectively. Delong's test indicated a statistically significant difference between the AUCs of VAI and CVAI (Z=5.51, P<0.001). The optimal cutoff value for VAI was 1.103, with sensitivity and specificity of 69.4% and 63.1%, respectively (Youden's index = 0.325). The optimal cutoff value for CVAI was 66.71, with sensitivity and specificity of 78.1% and 57.9%, respectively (Youden's index = 0.360) (Figure 1 [Figure 1: see original paper]). Kaplan-Meier survival analysis demonstrated that higher CVAI categories were associated with greater fatty liver risk (^{2}=1,153.06, P<0.001) (Figure 2 [Figure 2: see original paper]).

2.5 Stratified Analysis by Covariates

Further subgroup analysis by sex, age, and BMI showed that after adjusting for sex (except in sex-stratified analysis), age, BMI, systolic blood pressure, ALT,

AST, TG, TC, HDL-C, and LDL-C, the CVAI-Q4 group was associated with fatty liver incidence across all subgroups. However, in women, the CVAI-Q2 and CVAI-Q3 groups were not significantly associated with fatty liver (Table 3).

Discussion

This single-center retrospective cohort study of a physical examination population analyzed the association between baseline VAI and CVAI indices and incident fatty liver, and evaluated their predictive value using ROC curves. The results demonstrated that both baseline VAI and CVAI were significantly associated with fatty liver development, with CVAI showing superior predictive ability compared to VAI. These findings suggest that CVAI has good predictive value for fatty liver occurrence in Chinese populations.

The global prevalence of fatty liver continues to rise, with recent epidemiological data indicating a worldwide prevalence of approximately 30%. Fatty liver is often asymptomatic in its early stages, with many patients diagnosed incidentally during health examinations. A recent retrospective study analyzing health checkup data from 30 Chinese provinces between 2017 and 2022 found that among 5,757,335 adults who underwent liver transient elastography, the prevalence of fatty liver was 44.39%. High-risk groups included men, obese individuals, patients with diabetes, hypertension, dyslipidemia, metabolic syndrome, and those with elevated serum ALT or AST. Our retrospective cohort analysis of a physical examination population found that nearly 15% of non-fatty liver participants progressed to fatty liver over a mean follow-up of 2.7 years. Compared with those who did not develop fatty liver, participants who developed fatty liver had higher baseline age, BMI, systolic blood pressure, ALT, AST, TG, TC, and LDL-C, and lower HDL-C. Lifestyle changes, including diets high in sugar and fat and sedentary work patterns, have also contributed to the increased risk of fatty liver. Therefore, early screening and intervention for fatty liver are crucial to reduce its burden on individuals and society.

Obesity is an independent risk factor for fatty liver, with higher prevalence observed in obese populations compared to the general population. Recently, the European Association for the Study of Obesity (EASO) proposed a new framework for diagnosing, staging, and managing obesity in adults, emphasizing that excessive abdominal fat accumulation is a key risk factor for obesity-related complications. EASO recommends incorporating parameters that reflect visceral fat distribution for more effective management of obesity-related complications. Traditional obesity assessment indices such as waist circumference and BMI cannot accurately reflect body fat content and distribution. While CT and MRI are the gold standards for visceral fat measurement, their high cost, time requirements, and radiation exposure preclude routine clinical use. To address this, the VAI was developed in 2010 based on routinely measured clinical parameters including waist circumference, BMI, TG, and HDL-C, with its accuracy validated against imaging gold standards. However, recognizing that ethnic-

ity, age, and sex may influence visceral fat distribution, Chinese researchers proposed the population-specific CVAI in 2016, demonstrating its superiority over waist circumference, BMI, and VAI in assessing visceral fat distribution in Chinese populations.

Previous studies have shown that CVAI correlates with various metabolic diseases, including obesity, type 2 diabetes, and fatty liver. However, most research on CVAI and fatty liver has been cross-sectional, with few longitudinal cohort studies. Therefore, this study evaluated the relationship between VAI and CVAI with incident fatty liver in a physical examination cohort. The results indicate that both indices can effectively predict fatty liver development, with ROC analysis showing superior predictive performance for CVAI compared to VAI. Multivariate Cox regression analysis revealed that the CVAI-Q4, Q3, and Q2 groups had 3.375-fold (95%CI=2.488–4.576), 3.335-fold (95%CI=2.599–4.278), and 2.431-fold (95%CI=1.939–3.048) higher risks of fatty liver compared to the CVAI-Q1 group, respectively. Survival analysis showed that the fatty liver incidence in the CVAI-Q4 group was 8–10 times higher than in the CVAI-Q1 group over the follow-up period. These findings suggest that abnormal visceral fat accumulation, reflected by elevated CVAI, is closely associated with fatty liver risk in Chinese populations. With its higher AUC for fatty liver prediction compared to VAI, CVAI demonstrates important potential for early screening and risk assessment in large-scale Chinese populations.

Stratified analysis showed that the highest CVAI quartile was associated with fatty liver across different age and BMI subgroups. However, sex-stratified analysis revealed that in women, only the CVAI-Q4 group showed a significant association with fatty liver, while the CVAI-Q2 and CVAI-Q3 groups did not. This suggests that men may be more sensitive to changes in CVAI levels, while women may require higher CVAI levels to significantly increase fatty liver risk. Studies have consistently reported higher fatty liver incidence in men than in women, which aligns with our findings. This sex difference may be related to sex-specific fat distribution patterns: men tend to accumulate more visceral adipose tissue, while premenopausal women primarily accumulate subcutaneous fat. After menopause, women's fat distribution shifts toward visceral adiposity, potentially increasing metabolic disease risk. Therefore, interventions targeting visceral fat control are particularly important for men to reduce fatty liver and related metabolic disease risks. For women, especially postmenopausal women, higher CVAI thresholds may be needed to effectively identify fatty liver risk. However, our study had insufficient sample size for postmenopausal women, limiting in-depth analysis of this subgroup. Future studies should increase sample sizes of postmenopausal women to comprehensively evaluate CVAI's predictive efficacy in this population and further explore how sex differences affect CVAI's predictive performance.

This study has several limitations. First, our study population consisted primarily of healthy-weight individuals, with a relatively small proportion of obese participants. Second, while we adjusted for common confounders such as age,

blood pressure, and BMI, other potential confounders including dietary habits, physical activity, psychological factors, and environmental factors were not included in the analysis. Finally, CVAI was calculated only at baseline and may have changed during follow-up; the relationship between dynamic changes in CVAI and fatty liver risk warrants further investigation.

In conclusion, baseline CVAI is significantly associated with incident fatty liver, and its predictive ability is superior to that of VAI. These findings demonstrate that CVAI has good predictive value for fatty liver development in Chinese populations and is suitable for risk assessment in large-scale Chinese populations or physical examination cohorts.

Author Contributions: XU Hao was responsible for clinical data collection, organization, analysis, and drafting of the manuscript. FANG Da was responsible for creating figures and tables and assisting with statistical analysis. ZHOU Weihong was responsible for examination of the physical examination population. BI Yan contributed to manuscript revision and proofreading. GU Tianwei conceived the study, designed the research protocol, finalized the manuscript content, and takes responsibility for the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.