ORIGINAL RESEARCH

Relationships between Alanine Aminotransferase Levels, Abnormal Liver Echogenicity, and Metabolic Syndrome

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Background: **Elevated alanine aminotransferase (e-ALT) and abnormal liver echogenicity (ab-echo), as determined by sonography, have been linked to metabolic syndrome (MetS). However, which of these is more closely related to MetS, especially among older men, remains unknown.**

Methods: **Data from 3065 men aged 65 years or older who were undergoing a routine health examination and who were not taking any medications for MetS were analyzed retrospectively. The patients were divided into 4 groups: group N (n = 1228; patients have normal ALT and liver echogenicity); group A (n = 110; patients have e-ALT but normal liver echogenicity); group E (n = 1381; patients have ab-echo but normal ALT); group AE (n = 346; patients have both e-ALT and ab-echo).**

Results: **Among the 3065 subjects, 714 participants were found to have MetS (23.3%). It is not surprising that MetS components were highest in group AE. More interestingly, compared with group A, group E had higher levels of MetS components (except that high-density lipoprotein cholesterol levels were lower). Similar findings were confirmed by logistic regression. Group E had a significantly higher odds ratio of having MetS than group A (2.73; 95% CI, 1.565–4.763).**

Conclusions: **Our data confirm that both e-ALT and ab-echo are related to a higher incidence of MetS among Taiwanese older men. Of these 2 abnormalities, ab-echo seems to be more closely related to MetS. Further studies are needed to elucidate the complex relationships between these factors in other age and ethnic groups. (J Am Board Fam Med 2011;24:407–414.)**

Keywords: **Alanine Aminotransferase, Geriatrics, Liver Echogenicity, Metabolic Syndrome, Taiwan**

Metabolic syndrome (MetS), a growing public health problem all over the world, has been shown to be highly predictive for future cardiovascular disease (CVD) and type 2 diabetes mellitus. Although the clustering of these cardiovascular risk factors had been known for more than 80 years,[1] a formal name and definition for MetS was not proposed until 1998 by the World Health Organization.[2] Because of the requirement of measuring insulin resistance in this version of the MetS criteria, which is quite complicated to do, a more practical definition was proposed by the National Cholesterol Education Program Adult Treatment Panel III in 2001.[3] A further modification of this version in 2004 has now become the most commonly used definition for MetS[4,5] and is used in this study. Subjects with 3 or more of the following abnormalities fulfill the criteria of MetS: central obesity (elevated waist circumference [WC] ≥90 cm among Asian men); elevated triglyceride (TG) (≥150 mg/dL); reduced high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL for men); elevated blood pressure (systolic blood pressure [SBP] ≥130 mm Hg or diastolic blood pressure [DBP] ≥85 mm Hg); elevated fasting plasma glucose (FPG) concentration (≥100 mg/dL). At present,

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the prevalence of MetS is 25.1% in the United States, 16.4% in Taiwan, and is relatively high among older adults.[6]

Nonalcoholic fatty liver disease is one of the most common causes of elevated alanine aminotransferase (e-ALT). It can cause a broad spectrum of liver damage, ranging from simple steatosis to nonalcoholic steatohepatitis, advanced fibrosis, and even cirrhosis. At the same time, patients with type 2 diabetes also were found to have e-ALT levels.[7] This finding was further proved by Mainous et al[8] that the elevated r-glutamyl transpeptidase and e-ALT are associated with undiagnosed diabetes as well as impaired fasting glucose. Thus, in 2001 Marchesini et al[9] suggested that nonalcoholic fatty liver disease should be regarded as one of the features of MetS. Abdominal sonography is a commonly used tool during routine health examinations. Increased liver parenchymal echogenicity is a reliable criterion for diagnosing fatty liver.[10] Vehmas et al[11] reported that there was a significant correlation between increased liver echogenicity and elevated blood pressure and other features of MetS. It should be noted that the abovementioned studies were mostly conducted in adults. However, because the population is gradually aging worldwide, it is important and interesting to examine this issue in older adults.

Given the above evidence, it is logical to hypothesize that subjects with both e-ALT and abnormal liver echogenicity (ab-echo) should have higher likelihood of having MetS. In this study, we have not only evaluated the incidence of MetS in patient with either one or both of these 2 abnormalities, but also have tried to understand which one of them is more closely related to MetS.

Methods

Patients

This cross-sectional study enrolled male adults aged 65 years or older during a routine health checkup at the MJ Health Screening Center in Taiwan. MJ Health Screening Centers are private-membership clinics around Taiwan that provide regular health examinations to their members. In this study, the participants were all anonymous, and informed consent was obtained from the study subjects. The data were provided by MJ Health Screening Center for research purposes only, and this study protocol was also approved by the institutional review board of MJ Health Screening Center. There were 6021 men aged 65 years or older who had a routine health examination at the MJ Health Screening Center from January through December 2007. Those with significant major medical diseases; a history of diabetes, hypertension, or hyperlipidemia; or who were taking medications for these diseases or other medications known to affect glucose metabolism were all excluded (2890 patients; 48%). Furthermore, patients with a history of current or past excessive alcohol consumption (more than 20 g/day, on average) were also excluded (193 patients; 3.2%). Finally, 3065 subjects were eligible for analysis. It should be mentioned that, among these eligible patients, 288 (9.4%) and 104 (3.4%) had positive hepatitis B virus surface antigens (HBsAg) or antibodies to hepatitis C virus (anti-HCV), respectively.

Data Collection

Participants visited the clinic at 8 AM after at least a 10-hour fast. Information about medical history, lifestyle, alcohol intake, smoking, and physical exercise was obtained through an interview with senior nursing staff. A complete physical examination was conducted, and body mass index was calculated as weight/height^2 (kg/m^2). WC was taken at the midway point between the inferior margin of the last rib and the crest of the ilium, in a horizontal plane. SBP and DBP were measured by nursing staff using a computerized auto-mercury sphygmomanometer on the right arm of the participants, who had rested for 5 minutes in a sitting position.

A venous blood sample was collected for biochemistry study. Plasma was separated from blood within 1 hour and stored at −30°C. FPG, TG, total cholesterol, HDL-C, low-density lipoprotein cholesterol, aspartate aminotransferase, and ALT were measured.

An abdominal sonogram was performed and the results were interpreted for every participant by 3 well-experienced radiologists using a high-resolution B-mode scanner (SSA-240A, Toshiba Corporation, Tokyo, Japan). The radiologists had regular conferences to discuss all the radiologic results to reduce bias from different readers. The normal liver echogenicity was labeled as "0" and ab-echo was labeled as "1" based on liver-kidney echo discrepancy and loss of echoes from the walls of the portal veins.[12]

To compare the effect of e-ALT and ab-echo, the study cohort was divided into 4 groups:

- Group N (n = 1228): patients with both normal ALT and liver echogenicity
- Group A (n = 110): patients with e-ALT but normal liver echogenicity
- Group E (n = 1381): patients with ab-echo but normal ALT
- Group AE (n = 346): patients with both e-ALT and ab-echo

Statistical Analysis

Analysis was performed using SPSS software version 18.0 (IBM, Somers, NY). Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with Levene's test. Because this was a retrospectively designed study, the sample size could not be estimated before the study started, as is usually done in a prospective, randomized, controlled trial. Thus, the retrospective achieved power of an independent sample *t* test and one-way analysis of variance was calculated using SPSS general linear model procedures and that of the χ^2 test was obtained using G*Power 3.0.10 software (Heinrich Heine, University of Düsseldorf, Germany). Continuous variables are expressed as mean ± SD. Because of the nonnormal distribution, TG values were log transformed before analysis. An independent sample *t* test was used to evaluate the anthropometric data and metabolic parameters between patients with and without MetS. The percentage of participants with ab-echo was calculated, and the χ^2 test was used to compare the difference between these 2 groups. The odds ratios (ORs) for having MetS between groups were evaluated and compared by logistic regression. One-way analysis of variance with the Bonferroni test as the post hoc test was applied to compare the data between the 4 groups. Finally, linear trend test (using linear contrast in general linear model) was used to evaluate the trend of the mean of the number of MetS components in different groups.

All statistical tests were 2-sided, and $P < .05$ was considered to be statistically significant. In addition to providing the type I error rate ($\alpha = 0.05$), the retrospectively achieved power (equal to 1 minus the type II error rate) of each statistical test was provided.

Results

Among the 3065 participants, 714 patients (23.3%) were diagnosed as having MetS. The anthropometric variables, blood pressure, serum biochemistries, and results are shown in Table 1. There was no significant difference in age between patients with and without MetS (MetS+, MetS−, respectively). Not surprisingly, the MetS+ group had significantly higher body mass index, WC, SBP, DBP, FPG, total cholesterol, low-density lipoprotein cholesterol, log-transformed TG level, and ALT and lower HDL-C ($P < .001$). As for liver echogenicity, the percentage of participants with ab-echo was significantly higher in the MetS+ group compared with the MetS− group ($P < .001$).

Table 2 shows the mean of each MetS component in the 4 groups separately. All of these components, except HDL-C, were significantly higher when e-ALT, ab-echo, or both were present ($P < .001$). As expected, group AE had the highest level of MetS components compared with the other 3 groups (except in the case of HDL-C). However, it is interesting to note that, compared with group A, group E had more severe levels of MetS components. Figure 1 illustrates the mean number of MetS components in different groups. The trend increased when either e-ALT or ab-echo was present.

In Figure 2, the probabilities of having MetS in patients with e-ALT or ab-echo are demonstrated. The OR (95% CI) are shown (*upper line*) for patients with e-ALT. It should be stressed that this comparison was between patients with and without e-ALT and did not consider whether they had ab-echo. In other words, only one abnormality was evaluated at a time. The OR of patients with and without ab-echo were similarly compared (*lower line*). Because other studies in this area all had a similar design, this grouping method allowed us to compare our data with that from other studies. It is clear that both groups had a higher OR than their control counterparts. Moreover, from the figure, patients with ab-echo had a much higher risk of having MetS than patients with e-ALT.

Finally, compared with the normal group (group N), the OR for having MetS was significantly higher in groups E and AE ($P < .05$) (Figure 3). Here, it should be stressed that we excluded ab-echo in group A and e-ALT in group E, which is different from the comparisons in

Table 1. The Anthropometric and Metabolic Variables of Patients With or Without Metabolic Syndrome

	MetS(−)	MetS(+)	*P*	Power†
n	2351	714		
Age (years)	70.2 ± 4.8	70.3 ± 5.0	.577	0.086
Body mass index (kg/m^2)	22.7 ± 2.8	25.6 ± 2.7	<.001	1.000
Waist circumference (cm)	81.5 ± 7.9	91.0 ± 7.3	<.001	1.000
Systolic blood pressure (mm Hg)	130.0 ± 19.5	141.1 ± 17.1	<.001	1.000
Diastolic blood pressure (mm Hg)	74.2 ± 11.1	80.3 ± 11.0	<.001	1.000
Fasting plasma glucose (mg/dL)	100.8 ± 16.3	113.0 ± 27.0	<.001	1.000
Total cholesterol (mg/dL)	198.4 ± 33.2	204.3 ± 36.2	<.001	0.981
HDL-C (mg/dL)	54.4 ± 14.0	42.9 ± 10.7	<.001	1.000
LDL-C (mg/dL)	124.0 ± 30.2	127.5 ± 32.5	.009	0.772
Log TG	1.96 ± 0.18	2.19 ± 0.18	<.001	1.000
Liver echogenicity (abdominal sonogram)*	49%	79%	<.001	1.000
AST (U/L)	26.1 ± 16.5	26.9 ± 15.2	.241	0.216
ALT (U/L)	24.4 ± 22.4	28.6 ± 18.3	<.001	0.995

Data are shown as mean ± SD.
*χ^2 test was used.
†The retrospective power of an independent sample *t* test was calculated using SPSS general linear model procedures and that of the χ^2 test was obtained using G*Power 3.00.10 software (Heinrich Heine, University of Dusseldorf, Germany).
MetS(−), without metabolic syndrome; MetS(+), with metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Log TG, log transformation of triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Figure 2. Moreover, all the between-group comparisons reached statistical significance ($P < .05$), ie, group AE versus group E and group E versus group A.

Discussion

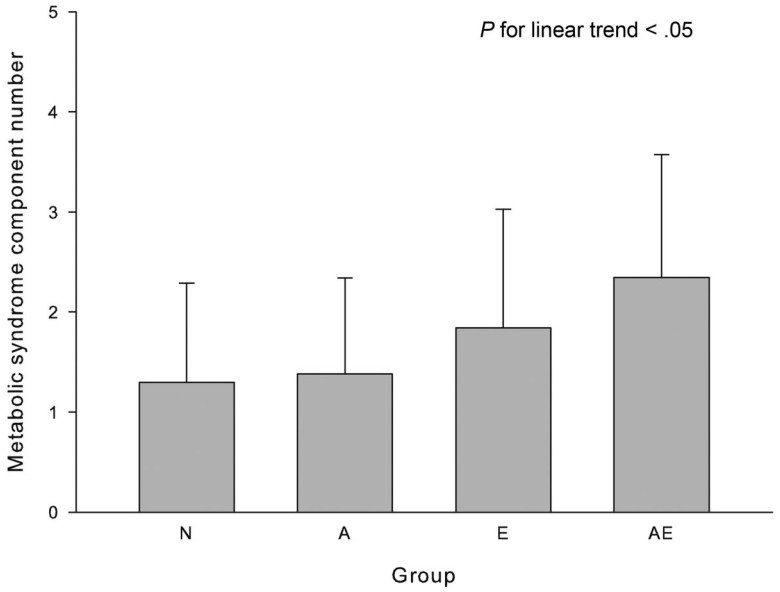
Both e-ALT and ab-echo were found to be related to MetS. Their relationships have been previously studied and documented in the literature.[11,13–17]

Table 2. Components of Metabolic Syndrome in Different Groups According to Alanine Aminotransferase Level and Liver Echogenicity

	Group N	Group A	Group E	Group AE	*P*	Power‖
n	1228	110	1381	346		
Age (years)	70.6 ± 5.1†§	70.5 ± 5.1	70.0 ± 4.7*	69.5 ± 4.6*	.001	0.952
BMI (kg/m^2)	22.1 ± 2.6†§	22.4 ± 2.8†§	24.1 ± 2.9*†§	25.0 ± 2.9*†‡	<.001	1.000
Waist (cm)	80.0 ± 7.9†§	80.5 ± 7.9†§	86.0 ± 8.3*†§	88.6 ± 8.0*†‡	<.001	1.000
SBP (mm Hg)	130.7 ± 20.3†§	130.4 ± 19.2	133.7 ± 19.0*	135.4 ± 18.1*	<.001	0.992
DBP (mm Hg)	74.1 ± 11.2†§	74.1 ± 10.7§	76.5 ± 11.3*	77.8 ± 11.3*†	<.001	1.000
FPG (mg/dL)	100.1 ± 13.8†§	103.2 ± 24.4§	105.3 ± 22.4*§	109.5 ± 24.2*†‡	<.001	1.000
TC (mg/dL)	197.3 ± 33.6†§	193.2 ± 37.3§	201.3 ± 33.3*	204.6 ± 36.2*†	<.001	0.977
HDL-C (mg/dL)	54.9 ± 14.7†§	54.6 ± 14.9†§	49.8 ± 13.1*†§	47.3 ± 13.8*†‡	<.001	1.000
LDL-C (mg/dL)	122.9 ± 30.0‡	117.8 ± 36.0†§	126.4 ± 30.3*†	127.6 ± 32.7†	.001	0.951
Log TG	1.95 ± 0.18†§	1.97 ± 0.20†§	2.05 ± 0.20*†§	2.12 ± 0.21*†‡	<.001	1.000

Data are shown as mean ± SD. Group N: normal ALT and liver echogenicity; group A: elevated ALT and normal liver echogenicity; group E: normal ALT and abnormal liver echogenicity; group AE: elevated ALT and abnormal liver echogenicity.
*$P < .05$ against group N.
†$P < .05$ against group A.
‡$P < .05$ against group E.
§$P < .05$ against group AE.
‖The retrospective power of one-way analysis of variance was calculated using SPSS general linear model procedures.
BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Log TG: log transformation of triglyceride.

Figure 1. This graph shows the mean of the number of metabolic syndrome components among the 4 groups. The Y axis shows the number of the metabolic syndrome components and the X axis shows the 4 different groups. Group N: normal alanine aminotransferase (ALT) and liver echogenicity; group A: elevated ALT and normal liver echogenicity; group E: normal ALT and abnormal liver echogenicity; group AE: elevated ALT and abnormal liver echogenicity.



Taiwan is a region with a high prevalence of hepatitis and hepatocellular carcinoma.[18] At the same time, the prevalence of MetS has increased in recent years, especially among older adults. Thus, the roles of e-ALT and ab-echo in MetS are vital. Surprisingly, a number of studies have indicated

Figure 2. This graph shows the odds ratio of having metabolic syndrome among subjects with normal and elevated alanine aminotransferase (e-ALT) (*upper line*), and among subjects with normal and abnormal liver echogenicity (ab-echo) (*lower line*). The numbers of patients with normal and e-ALT were 2609 and 456, respectively; patients who had normal and ab-echo were 1338 and 1727, respectively. It should be noted that the comparison between patients with normal and e-ALT (*upper line*) did not consider whether they had ab-echo. Similarly, the comparison between patients with normal and ab-echo (*lower line*) did not consider whether they had e-ALT. In other words, only one abnormality was evaluated at a time.

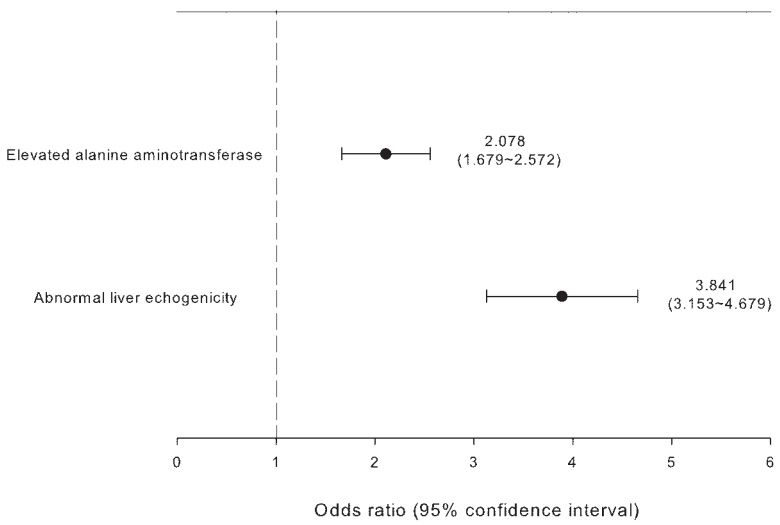
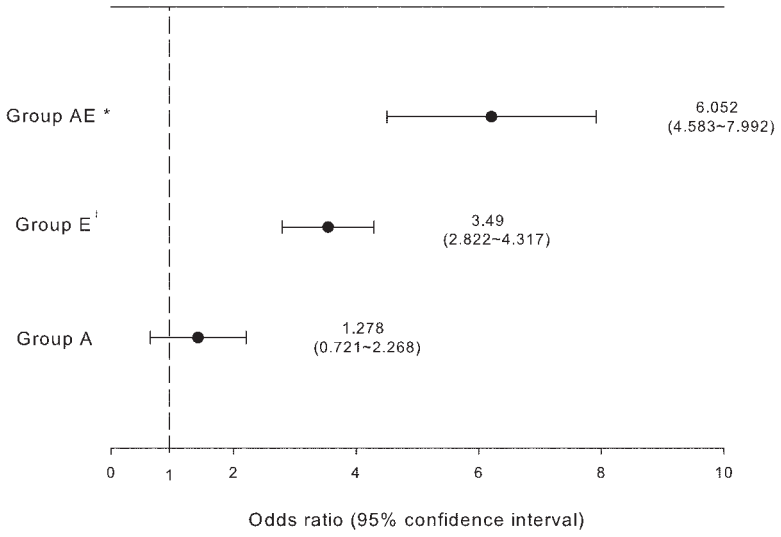


Figure 3. Odds ratio for having metabolic syndrome between different groups. The *upper line* shows group AE compared with group N; the *middle line* shows group E compared with group N; and the *lower line* shows group A compared with group N. Group N: normal alanine aminotransferase (ALT) and liver echogenicity; group A: elevated ALT and normal liver echogenicity; group E: normal ALT and abnormal liver echogenicity; group AE: elevated ALT and abnormal liver echogenicity. All have a significance of $P < .05$. *Odds ratio, 1.734 (95% CI, 1.361–2.209) between groups AE and E; †Odds ratio, 2.73 (95% CI, 1.565–4.763) between groups E and A.



that these 2 abnormalities do not always occur concomitantly.[19,20] For instance, it is possible to have e-ALT but with normal liver echogenicity. Thus, the question has been raised as to which factor is more closely related to MetS. The present study was performed to investigate this dilemma. Although similar studies have been performed in the past, most of them focused only on one abnormality. Moreover, to our knowledge, none of these studies focused on older adults. In addition, it should also be noted that we excluded patients already taking medication for MetS, a point that was seldom noted in other similar studies.[9,11,14,15,17,21] Although these more stringent exclusion criteria should give us more accurate results, at the same time, some subjects with treated MetS components also were excluded. Therefore we were unable to observe more extreme cases on the MetS spectrum, and we expected to underestimate the relationships between the observed parameters. On the other hand, a positive result could be taken as more solid evidence to support our findings. Our data suggests that patients with abecho would have higher likelihood of having MetS than those with e-ALT. At the same time, it is not surprising that patients with both abnormalities have the highest risk of having MetS.

To our knowledge, the earliest study focusing on the relationship between e-ALT and MetS was published in 2004.[14] Hanley et al[14] showed that e-ALT was significantly related to MetS in the Insulin Resistance Atherosclerosis Study. They found that every 4.17-U/L increase in ALT would result in a 1.43 times higher risk of having MetS. Using a similar calculation, in our study, the group with abnormal ALT had ALT levels 36.2 U/L higher than in the normal group (normal ALT mean, 20 U/L; e-ALT mean, 56.2 U/L). It can be estimated that, with the same increase in ALT (4.17 U/L in Hanley's study), the OR was only 0.24 times higher. This finding suggests that the effect of e-ALT might be less important among elderly Taiwanese people than among whites. It should be noted that the Insulin Resistance Atherosclerosis Study was a longitudinal study, and the observation of the effect of ALT was conducted in patients with normal liver enzymes. However, 2 later studies conducted among Korean and Taiwanese populations had much closer ORs for patients with e-ALT compared with ours, although the average age of the participants was lower.[15,16] These slight differences in the ORs might be because of differences in age or ethnicity. From the above evidence, the conclusion that e-ALT is closely related to MetS can be confirmed.

Increased parenchymal echogenicity is a reliable criterion for diagnosing fatty liver.[10] This kind of fat accumulation in the liver is a marker of hepatic insulin resistance and thus correlates closely with all MetS components.[22] One of the largest studies in this area was conducted in a Korean population by Kim et al.[15] Based on the findings of the ultrasonography, patients were divided into 4 groups according to the severity of steatosis (absent, mild, moderate, and severe) in that study. Compared with the normal control (absent group), the ORs for the other 3 groups of having MetS were 2.43, 4.54, and 7.32, respectively. A similar study in an adult Taiwanese population by Shen et al,[16] with only 2 groups divided according to liver echogenicity, showed that the OR in the ab-echo group was 3.46. This finding was very close to our result. Together, although the ORs might vary, these studies further support our finding of a positive relationship between ab-echo and MetS among Taiwanese older men.

An interesting phenomenon—that e-ALT and ab-echo do not usually occur simultaneously—has been noted since 2003.[19,20] The Dallas Heart Study showed that only 21% of patients with hepatic steatosis had e-ALT,[23] which is very similar to the percentage in our cohort (20%; data not shown). On the other hand, as many as 60% of subjects with e-ALT were also found to have ab-echo in the survey done by Shen.[16] Again, this value is quite close to our finding (75.9%; data not shown). Given the fact that patients with ab-echo had greater likelihood of having e-ALT or MetS, we can conclude that ab-echo might be a more sensitive marker for MetS than e-ALT, especially among Taiwanese older adults. This evidence supports the hypothesis that the accumulation of fat in the liver cells, which can be detected by sonography, must exist for a certain period of time before it can cause clinical e-ALT.

There are certain limitations to our study that should be considered. First, this was a cross-sectional study and therefore provided less consolidated evidence than would a longitudinal or well-designed epidemiologic study. Second, liver biopsy is the gold standard for diagnosing fatty liver, although, in reality, it would not be feasible for each of the participants to undergo this invasive procedure. Furthermore, the use of ab-echo can be justified by the high concordance in diagnostic rate between sonography and liver biopsy for liver steatosis.[24] Third, because this study was conducted in one ethnic group, the generalizability of the results is limited. Similar studies are needed among different ethnic groups to further support our findings. Finally, as mentioned in the Methods section, some subjects had positive HBsAg (9.4%) or anti-HCV (3.4%). At present, evidence suggests that hepatitis C virus infection is related to MetS.[25,26] However, little is known about the role of hepatitis B virus infection and MetS. We did not exclude these patients because the purpose of the study was only to observe the effect of both e-ALT and ab-echo on MetS, regardless of the cause. At the same time, our data also showed that the incidence of positive HBsAg and anti-HCV was lower among patients with MetS than those without (HBsAg, 9.1% vs 9.5%, respectively; anti-HCV, 3.1% vs 3.5%, respectively). Even with these 4 limitations, we would like to emphasize that this is the first study to explore the importance of the role of e-ALT and ab-echo in MetS in older adults after excluding confounding treatments.

Conclusions

Our data confirms that both e-ALT and ab-echo are related to a higher incidence of MetS in Taiwanese older men. Of these 2 abnormalities, ab-echo seems to be more closely related to MetS. Further studies are needed to elucidate the complex relationships between these factors in other age and ethnic groups.

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