Original Article

Longitudinal Changes in Liver Aminotransferases Predict Metabolic Syndrome in Chinese Patients with Nonviral Hepatitis

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Abstract

Objective This study explored the correlation of longitudinal changes in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels with the incidence of metabolic syndrome (Mets) based on a dynamic health examination cohort.

Methods A Mets-free dynamic cohort involving 4541 participants who underwent at least three health examinations from 2006 to 2011 was included in the study. Mets was defined according to the Chinese Medical Association Diabetes Branch definition that included hypertension, obesity, hyperlipidemia, and hyperglycemia. Generalized estimating equation (GEE) model was used to analyze multivariate relative risk (RR) of repeated observations of ALT and AST in quartiles for Mets or its components according to gender.

Results In all, 826 Mets cases were reported. Adjustment of relevant parameters indicated that time-varying changes in ALT and AST levels were positively associated with the incidence of Mets in a dose-response manner. Positive association between high ALT levels and fatty liver was much stronger than that between high AST levels and fatty liver, particularly in male participants. These associations were consistently observed in the following subgroups: participants with ALT and AST levels of <40 U/L, participants with of <25 kg/m^2, and participants with non-fatty liver. Furthermore, participants with 2 Mets components at baseline showed lower multivariate adjusted RRs of ALT and AST for Mets than participants with 0-1 Mets component.

Conclusion These results suggested that elevated serum ALT and AST levels were early biomarkers of Mets or its components.

Key words: Alanine aminotransferase; Aspartate aminotransferase; Metabolic syndrome; Dynamic cohort study; Generalized estimating equation model

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INTRODUCTION

Metabolic syndrome (Mets), which is characterized by various metabolic disorders (hypertension, hyperlipidemia, obesity, and hyperglycemia), is an important risk factor for cardiovascular diseases and all-cause mortality[1-2]. The prevalence of Mets is increasing in China in recent decades because of the spread of the western lifestyle and increase in life

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expectancy[3]. It is very important to prevent and control Mets in its early stage in different patient groups in China through targeted measures.

Some epidemiological studies[4] have used increasing levels of serum liver aminotransferases, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as surrogate markers of nonalcoholic fatty liver disease (NAFLD). Recent studies suggest that NAFLD is a hepatic expression of Mets at an early stage[5-6]. Increased levels of liver aminotransferases are associated with vascular endothelial disorders and body insulin sensitivity, which is independent of obesity[7-8]. Moreover, association between elevated ALT and AST levels and Mets has been reported[9-12].

Till date, the association of serum ALT and AST levels with the incidence of Mets has not been confirmed in cross-sectional studies[10,13]. Furthermore, although AST and ALT levels may vary over time, existing cohort studies have ignored the changes in serum ALT and AST levels during follow-up and have only analyzed the association between baseline ALT and AST levels and incidence of Mets[14]. Therefore, it is unclear whether high serum ALT and AST levels are associated with the incidence of Mets.

Moreover, various metabolic conditions may affect the association between ALT and AST levels and incidence of Mets. In addition, there is no consensus on whether sequential changes in ALT and AST levels within the reference range can predict Mets.

To clarify the relationship between ALT and AST and the incidence of Mets, the study used a dynamic health examination cohort study in Dongying City, China, which included repeated observations on the same sample. Data were analyzed using the generalized estimating equation (GEE) model that helps in analyzing inherent correlations in data, in handling unbalanced and incomplete data, and in characterizing changes in variables overtime in longitudinal data; moreover, the GEE model is free of distributional assumption[15]. Thus, in this dynamic longitudinal study, we investigated the association of time-varying changes in serum ALT and AST levels with Mets in different subgroups to determine whether serum liver aminotransferases were biomarkers of Mets.

MATERIALS AND METHODS

Study Population

This study was performed at a general hospital in Dongying City, China, from January 2006 to December 2011. Annual health examination including analysis of physical characteristics and comorbidities, assessment of previous surgeries, analysis of biochemical characteristics, and color Doppler ultrasonography, was performed in a unified manner. In all, 5856 participants who underwent at least three intact health examinations during January 2006 to December 2011 and who agreed to provide their data for analysis were recruited. Data of each participant's first health examination was used as baseline data. In total, 226 participants who did not have data on aminotransferase tests at baseline, 803 participants who had Mets at baseline according to the Chinese Medical Association Diabetes Branch (CDS) definition, 29 participants who had (at baseline) or developed (during follow-up) severe systemic diseases such as congestive heart failure and renal failure, 244 participants who showed positivity for hepatitis B virus surface antigen, 8 participants who showed positivity for hepatitis C virus antibody, and 5 participants with hepatitis A infection during follow-up were excluded from the study. Thus, 4541 participants aged 24-75 years were included in the study.

General Examination

Standardized Interviews During each health examination, medical examiners performed standardized interviews to obtain the following information: age (in years); behavior, including smoking and drinking; medical history (cardiovascular diseases, metabolic diseases, kidney diseases, liver diseases, and so on); and prescription medication use (excluding medication such as antihypertensives, antihyperlipidemic and antihyperglycemic drugs, and hepatotoxicity medication on the day of the health examination; n=5). Participants were asked to report current smoking behavior and alcohol intake over the month before the study. Smoking was defined as smoking any tobacco product continuously or accumulatively for >6 months and at least once a day in the previous 30 days[16]. Drinking was defined as consumption of any type of alcoholic beverage once a week, excluding occasionally drinking during festivals[17].

Anthropometric Variables Anthropometric variables, including weight, height, and blood pressure, were analyzed. Weight and height were measured by asking the participants to wear light clothes and no shoes. Body mass index (BMI) was calculated by dividing the weight (in kilograms) by

the square of height (in meters). Blood pressure (BP) was measured from the right arm in a sitting position after asking the participants to relax for at least 5 min. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded twice by using mercury sphygmomanometers. Anthropometric measures were obtained by unified trained examiners to control interobserver variability.

Laboratory Analysis Blood samples were collected through venipuncture in the morning after overnight fasting (at least 12 h). The blood samples were centrifuged, refrigerated at the examination site, and sent for examination within 4 h. Fasting blood glucose (FBG, mmol/L) was measured using the glucose oxidase method. Total cholesterol (T-CH, mmol/L), triglyceride (TG, mmol/L), ALT (U/L), AST (U/L), and γ-glutamyltransferase (GGT, U/L) levels were measured using enzymatic methods.

Assessment of Fatty Liver Fatty liver was diagnosed by performing abdominal ultrasonography. The results were interpreted for every participant by two well-experienced radiologists.

Definition of Mets CDS criteria were adopted for defining Mets in the present study[18]. Participants were diagnosed with Mets if they had at least three of the following four risk factors: (1) overweight or obesity (BMI ≥25.0 kg/m^2), (2) hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg, or history of hypertension), (3) hyperlipidemia [fasting TG ≥1.7 mmol/L (110 mg/dL) or fasting high-density lipoprotein cholesterol (HDL-C) <0.9 mmol/L (35 mg/dL)], (4) hyperglycemia [FPG ≥6.1 mmol/L (110 mg/dL), 2-h post-meal glucose ≥7.8 mmol/L (140 mg/dL), or history of hyperglycemia].

Statistics

Statistical analysis was performed using SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC, USA). Serum ALT and AST levels were shown as quartiles: (1) ALT: <16, 17-22, 23-34, and 35-728 U/L for male participants and <10, 11-13, 14-19, and 20-441 U/L for female participants at baseline and (2) AST: <18, 19-22, 23-27, and 28-725 U/L for male participants and <15, 16-18, 19-21, and 22-245 U/L for female participants at baseline. ALT and AST levels in each participant during follow-up were categorized using the same quartiles as those used for baseline ALT and AST levels. Data for continuous variables are expressed as mean±standard deviation, and data for classified variables are expressed as percentages (%) in summary statistics. Analysis of variance (ANOVA) and chi-square test were used to determine differences in the continuous and classified variables, respectively. Trends for each variable with increasing ALT and AST grading were evaluated using Spearman's rank correlation analysis.

The GEE model was used to evaluate the independent effect of ALT and AST levels on the incidence of Mets or its components. Considering of gender difference, the associations of serum aminotransferase and prevalence of Mets was analyzed in males and females separately. Three models were used in the GEE analysis: a crude model (model 1), an age-and GGT-adjusted model (model 2), and a multivariate (including age, GGT, TBIL, T-CH, smoking, and drinking)-adjusted model (model 3). A simple GEE model was first used to identify factors associated with Mets, and multiple GEE model was next used to detect the association between AST levels and Mets. Variables that were significant at 0.10 (α) level in the simple GEE model were used in the multiple GEE model to adjust potential confounding factors. Quasi-likelihood under independence model criterion (QIC) was used to evaluate the goodness of fit of the GEE model. The statistic of QIC in model 3 was the smallest among the three models, indicating it had the best goodness of fit. Age was regarded as the underlying timescale, with entry time being the participant's age during the first health examination and exit time being the participant's age at the diagnosis of Mets or end of the health examination. Because levels of aminotransferases and other potential covariates changed over time, the GEE model analyzed repeated observations of both the aminotransferases and potential covariates from baseline to follow-up instead of analyzing baseline variables, as that performed in previous cohort studies. Serum ALT and AST levels were divided into quartiles, and the lowest category was used as the reference. Relative ratios and profile likelihood confidence intervals were calculated. Ordinal categorical variables of 1, 2, 3, and 4 for each quartile of serum ALT and AST levels were used to calculate *P* values for linear trends. The GEE models used 'logit' as the link function, and $P<0.05$ was considered significant.

Ethics Statement

The Ethics Committee of the School of Publich Health, Shandong University, approved this study. Informed oral consent was obtained from each participant. Participants were notified that their health examination data would be used for research

without leaking their private information (including name and contact information).

RESULTS

During 19,822 person-years of follow-up, 682 male participants, and 144 female participants developed Mets. The median duration of follow-up was 4.55 years.

The cohort was dichotomized into 2 groups based on gender. Demographic and biochemical parameters of the participants at baseline according to serum ALT and AST levels in male and female participants are listed in Tables 1-4.

Analysis of the association between serum ALT and AST levels and incidence of Mets in male participants (Table 5), with an increase in ALT grading, showed that the crude RR for Mets increased in a dose-dependent manner from the second to the fourth quartiles (model 1). Furthermore, we analyzed the relationship between changes in serum ALT levels and incidence of Mets after adjusting for age, GGT, smoking, and drinking (model 2), followed by adjustment of more relevant

Table 1. Baseline Characteristics of the Male Participants According to Serum ALT Quartiles

Parameters	ALL (*n*=2904)	Q1 of ALT (*n*=796)	Q2 of ALT (*n*=681)	Q3 of ALT (*n*=736)	Q4 of ALT (*n*=691)	*P* for ANOVA or Chi-square	*P* for trend
Continuous Variables ($\bar{x} \pm s$)							
Age	41.47±9.91	42.29±11.20	42.16±10.43	41.85±9.35	39.78±7.82	<0.001	<0.001
BMI	24.39±3.26	22.94±3.44	24.14±3.17	25.16±2.65	25.76±2.66	<0.001	<0.001
SBP	122.89±16.46	120.62±16.22	123.28±17.62	124.19±16.26	123.82±14.90	<0.001	<0.001
DBP	79.89±11.33	78.27±10.72	79.48±11.78	80.86±10.53	81.24±11.87	<0.001	<0.001
FBG	5.11±0.87	5.08±1.06	5.12±0.93	5.18±0.99	5.25±0.92	0.005	<0.001
TG	1.89±1.56	1.58±1.41	1.82±1.53	1.99±1.60	2.37±1.90	<0.001	<0.001
HDL-C	1.15±0.22	1.22±0.21	1.16±0.21	1.11±0.21	1.11±0.20	<0.001	<0.001
T-CH	4.87±0.90	4.65±0.81	4.80±0.83	4.97±0.91	5.14±0.99	<0.001	<0.001
TBIL	14.09±5.96	14.51±6.36	14.14±5.76	13.75±5.50	13.81±6.03	0.265	-
Cr	96.22±9.51	95.06±9.89	97.00±9.33	96.09±9.20	96.86±9.41	0.565	-
GGT	34.16±33.90	20.66±11.89	25.84±17.15	33.77±23.13	58.96±54.02	<0.001	<0.001
WBC	6.38±1.50	6.11±1.37	6.36±1.44	6.43±1.54	6.64±1.55	0.025	<0.001
Classified Variables (percentage)							
Smoking	910/2904 (31.3%)	238/796 (30.0%)	208/681(30.5%)	220/736 (29.9%)	244/691 (35.3%)	<0.001	0.023
Drinking	1543/2904 (53.1%)	387/796 (48.6%)	345/681 (50.7%)	393/736 (53.4%)	418/691 (60.5%)	0.001	<0.001
ALT<40 U/L	2410/2904 (83.0%)	796/796 (100.0%)	681/681 (100.0%)	736/736 (100.0%)	197/691 (28.5%)	<0.001	<0.001
AST<40 U/L	2711/2904 (93.4%)	787/796 (98.9%)	666/681 (97.8%)	714/736 (97.0%)	544/691 (78.7%)	<0.001	<0.001
No fatty liver	2795/2904 (96.2%)	788/796 (99.0%)	661/681 (97.1%)	702/736 (95.4%)	650/691 (94.1%)	<0.001	<0.001
Mets' Components							
Hypertension	638/2904 (22.0%)	170/796 (21.4%)	148/681 (21.7%)	176/736 (23.9%)	146/691 (21.1%)	0.447	-
Obesity	1175/2904 (40.5%)	196/796 (24.6%)	268/681 (39.4%)	356/736 (48.4%)	355/691 (51.4%)	<0.001	<0.001
Hyperlipidemia	1054/2904 (36.3%)	187/796 (23.5%)	221/681 (32.5%)	288/736 (39.1%)	358/691 (51.8%)	<0.001	<0.001
Hyperglycemia	98/2904 (3.4%)	27/796 (3.4%)	22/681 (3.2%)	28/736 (3.8%)	21/691 (3.0%)	0.476	-
Numbers of Mets' Components						<0.001	<0.001
1 Mets component	864/2904 (29.8%)	367/796 (46.1%)	220/681 (32.3%)	167/736 (22.7%)	110/691 (15.9%)		
2 Met components	1017/2904 (35.0%)	268/796 (33.7%)	241/681 (35.4%)	266/736 (36.1%)	242/691 (35.0%)		
No Mets component	975/2904 (33.6%)	156/796 (19.6%)	209/681 (30.7%)	291/736 (39.5%)	319/691 (46.2%)		

Note. BMI, body mass index; Cr, serum creatinine; DBP, diastolic blood pressure; FBG, fasting blood glucose; GGT, γ-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TBIL, total bilirubin; T-CH, total cholesterol; TG, triglyceride; WBC, white blood cells.

Table 2. Baseline Characteristics of Female Participants According to Serum ALT Quartiles

Parameters	All (1637)	Q1 of ALT (466)	Q2 of ALT (371)	Q3 of ALT (424)	Q4 of ALT (376)	*P* for ANOVA or Chi-square	*P* for Trend
Continuous Variables ($\bar{x} \pm s$)							
Age	40.05±9.25	37.47±8.20	40.53±9.22	40.86±9.81	41.88±9.21	0.002	<0.001
BMI	22.13±2.96	21.28±2.49	21.96±2.92	22.41±2.84	23.07±3.34	<0.001	<0.001
SBP	115.65±16.91	112.60±13.21	116.13±17.13	117.32±18.45	117.19±18.55	<0.001	0.020
DBP	74.04±10.46	72.67±10.08	73.91±10.21	75.19±11.13	74.60±10.24	<0.001	0.005
FBG	4.92±0.72	4.80±0.48	4.91±0.86	4.89±0.57	5.08±0.92	<0.001	<0.001
TG	1.59±1.48	1.34±1.34	1.43±1.38	1.60±1.45	2.03±1.66	<0.001	<0.001
HDL-C	1.31±0.27	1.33±0.25	1.45±0.22	1.29±0.28	1.24±0.28	<0.001	0.001
T-CH	4.64±0.84	4.41±0.79	4.67±0.78	4.71±0.82	4.81±0.92	<0.001	<0.001
TBIL	11.69±5.03	11.47±4.98	11.65±5.22	11.79±4.74	11.89±5.24	0.201	-
Cr	80.73±9.65	80.81±8.93	80.94±9.00	79.79±10.29	81.36±10.23	0.016	0.030
GGT	15.73±13.86	11.35±3.48	12.85±4.77	14.31±6.01	24.96±24.63	<0.001	<0.001
WBC	5.76±1.49	5.62±1.53	5.69±1.39	5.85±1.56	5.89±1.47	0.045	0.037
Classified Variables (percentage)							
Smoking	9/1637 (0.6%)	2/466 (0.4%)	1/371 (0.3%)	1/424 (0.2%)	5/376 (1.3%)	<0.001	0.131
Drinking	20/1637 (1.2%)	2/466 (0.4%)	4/371 (1.1%)	4/424 (0.9%)	10/376 (2.7%)	<0.001	0.008
ALT<40 U/L	1586/1637 (96.9%)	466/466 (100.0%)	371/371 (100.0%)	424/424 (100.0%)	325/376 (86.4%)	<0.001	<0.001
AST<40 U/L	1616/1637 (98.7%)	466/466 (100.0%)	371/371 (100.0%)	424/424 (100.0%)	355/376 (94.4%)	<0.001	<0.001
No Fatty liver	1618/1637 (98.8%)	463/466 (99.4%)	370/371 (99.7%)	417/424 (98.3%)	368/376 (97.9%)	<0.001	0.005
Mets' Components							
Hypertension	180/1637 (11.0%)	33/466 (7.1%)	41/371 (11.1%)	57/424 (13.4%)	49/376 (13.0%)	0.015	0.002
Obesity	275/1637 (16.8%)	46/466 (9.9%)	57/371 (15.4%)	83/424 (19.6%)	89/376 (23.7%)	<0.001	<0.001
Hyperlipidemia	394/1637 (24.1%)	74/466 (15.9%)	77/371 (20.8%)	99/424 (23.3%)	144/376 (38.3%)	<0.001	<0.001
Hyperglycemia	38/1637 (2.3%)	3/466 (0.6%)	5/371 (1.3%)	7/424 (1.7%)	23/376 (6.1%)	0.012	<0.001
Numbers of Mets' components						<0.001	<0.001
1 Mets component	933/1637 (57.0%)	326/466 (70.0%)	221/371 (59.6%)	235/424 (55.4%)	151/376 (40.2%)		
2 Mets components	509/1637 (31.1%)	120/466 (25.8%)	120/371 (32.3%)	126/424 (29.7%)	143/376 (38.0%)		
No Mets component	189/1637 (11.5%)	18/466 (3.9%)	30/371 (8.1%)	60/424 (14.1%)	81/376 (21.5%)		

Table 3. Baseline Characteristics of Male Participants According to Serum AST Quartiles

Parameters	All (2904)	Q1 of AST (812)	Q2 of AST (767)	Q3 of AST (669)	Q4 of AST (656)	*P* for ANOVA or Chi-square	*P* for Trend
Continuous Variables ($\overline{x} \pm s$)							
Age	41.47±9.91	40.89±10.55	41.91±10.60	41.67±9.75	41.44±8.23	<0.001	0.129
BMI	24.39±3.26	23.62±3.32	24.36±3.41	24.74±2.88	25.18±3.08	<0.001	<0.001
SBP	122.89±16.46	121.65±16.65	122.86±16.97	123.33±15.75	124.29±16.15	<0.001	0.064
DBP	79.89±11.33	78.33±12.02	79.80±10.46	80.11±9.80	82.04±12.52	<0.001	<0.001
FBG	5.11±0.87	5.05±0.96	5.11±0.92	5.05±0.62	5.21±0.88	0.001	<0.001
TG	1.89±1.56	1.45±1.11	1.90±1.46	1.99±1.71	2.38±1.87	<0.001	<0.001
HDL-C	1.15±0.22	1.14±0.20	1.14±0.22	1.15±0.17	1.15±0.22	0.514	-
T-CH	4.87±0.90	4.66±0.79	4.82±0.90	4.92±0.88	5.17±0.98	<0.001	<0.001
TBIL	14.09±5.96	14.23±6.38	13.81±5.30	14.25±6.09	14.08±6.04	0.040	0.915
Cr	96.22±9.51	95.83±9.35	96.14±9.73	95.49±9.92	97.31±8.94	0.318	-
GGT	34.16±33.90	23.05±12.09	28.01±20.02	33.99±25.21	55.95±56.21	<0.001	<0.001
WBC	6.38±1.50	6.33±1.52	6.34±1.51	6.32±1.47	6.52±1.49	0.045	0.133
Classified Variables (percentage)							
Smoking	910/2904 (31.3%)	228/812 (28.1%)	242/767 (31.6%)	202/669 (30.2%)	237/656 (36.1%)	<0.001	0.023
Drinking	1543/2904 (53.1%)	377/812 (46.4%)	400/767 (52.2%)	364/669 (54.4%)	403/656 (61.4%)	<0.001	<0.001
ALT<40 U/L	2375/2904 (81.8%)	794/812 (97.8%)	730/767 (95.2%)	560/669 (83.7%)	291/656 (44.4%)	<0.001	<0.001
AST<40 U/L	2746/2904 (94.6%)	812/812 (100.0%)	767/767 (100.0%)	669/669 (100.0%)	498/656 (75.9%)	<0.001	<0.001
No Fatty liver	2795/2904 (96.2%)	794/812 (97.8%)	745/767 (97.1%)	632/669 (94.5%)	624/656 (95.1%)	<0.001	<0.001
Mets' Components							
Hypertension	638/2904 (22.0%)	163/812 (20.1%)	170/767 (22.2%)	144/669 (21.5%)	161/656 (24.5%)	0.218	-
Obesity	1169/2904 (40.3%)	285/812 (35.1%)	304/767 (40.2%)	282/669 (42.2%)	298/656 (45.4%)	<0.001	<0.001
Hyperlipidemia	1053/2904 (36.3%)	197/812 (24.3%)	281/767 (39.6%)	235/669 (35.1%)	340/656 (51.8%)	<0.001	<0.001
Hyperglycemia	98/2904 (3.4%)	30/812 (3.7%)	25/767 (3.3%)	18/669 (2.7%)	25/656 (3.8%)	0.130	-
Numbers of Mets' Components						<0.001	<0.001
1 Mets component	863/2904 (29.7%)	328/812 (40.4%)	232/767 (30.2%)	192/669 (28.7%)	111/656 (16.9%)		
2 Mets components	1014/2904 (34.9%)	273/812 (33.6%)	270/767 (35.2%)	245/669 (36.6%)	226/656 (34.5%)		
No Mets component	972/2904 (33.5%)	201/812 (24.8%)	255/767 (33.2%)	217/669 (32.4%)	299/656 (45.6%)		

Table 4. Baseline Characteristics of Female Participants According to Serum AST Quartiles

Parameters	All (1637)	Q1 of AST (472)	Q2 of AST (445)	Q3 of AST (318)	Q4 of AST (402)	*P* for ANOVA or Chi-square	*P* for Trend
Continuous Variables ($\bar{x}\pm s$)							
Age	40.05±9.25	37.58±8.05	39.73±9.20	42.01±10.49	41.78±8.89	<0.001	<0.001
BMI	22.13±2.96	21.71±2.67	22.03±3.14	22.38±2.93	22.54±3.04	<0.001	0.001
SBP	115.65±16.91	114.02±15.09	114.38±15.09	118.60±19.37	116.67±18.40	<0.001	0.036
DBP	74.04±10.46	73.15±10.14	73.11±10.98	75.84±10.35	74.69±10.17	<0.001	0.001
FBG	4.92±0.72	4.87±0.83	4.87±0.51	4.95±0.76	5.01±0.75	<0.001	<0.001
TG	1.59±1.48	1.21±1.12	1.44±1.32	1.78±1.60	2.12±1.78	<0.001	<0.001
HDL-C	1.31±0.27	1.34±0.28	1.31±0.29	1.36±0.28	1.29±0.25	0.035	0.006
T-CH	4.64±0.84	4.43±0.77	4.67±0.84	4.74±0.77	4.85±0.94	<0.001	<0.001
TBIL	11.69±5.03	11.29±4.91	11.89±5.04	12.00±5.23	11.68±5.00	0.181	-
Cr	80.73±9.65	81.27±8.36	80.43±9.67	79.60±10.12	81.22±10.43	0.383	-
GGT	15.73±13.86	12.69±4.78	13.65±7.10	15.50±8.91	22.36±24.76	<0.001	<0.001
WBC	5.76±1.49	5.84±1.51	5.73±1.56	5.85±1.41	5.63±1.48	0.068	-
Classified Variables (percentage)							
Smoking	9/1637 (0.6%)	1/472 (0.2%)	1/445 (0.2%)	2/318 (0.6%)	5/402 (1.2%)	0.101	-
Drinking	20/1637 (1.2%)	1/472 (0.2%)	3/445 (0.7%)	7/318 (2.2%)	9/402 (2.2%)	0.135	-
ALT<40 U/L	1586/1637 (96.9%)	472/472 (100.0%)	445/445 (100.0%)	318/318 (100.0%)	351/402 (87.3%)	<0.001	<0.001
AST<40 U/L	1616/1637 (98.7%)	472/472 (100.0%)	445/445 (100.0%)	318/318 (100.0%)	381/402 (94.8%)	<0.001	<0.001
No fatty liver	1618/1637 (98.8%)	469/472 (99.4%)	437/445 (98.2%)	315/318 (99.1%)	397/402 (98.8%)	<0.001	0.490
Mets' Components							
Hypertension	180/1637 (11.0%)	41/472 (8.7%)	31/445 (7.0%)	54/318 (17.0%)	50/402 (12.4%)	0.075	-
Obesity	275/1637 (16.8%)	64/472 (13.6%)	67/445 (15.1%)	65/318 (20.4%)	79/402 (19.7%)	<0.001	0.004
Hyperlipidemia	394/1637 (24.1%)	69/472 (14.6%)	95/445 (21.3%)	85/318 (26.7%)	144/402 (35.8%)	<0.001	<0.001
Hyperglycemia	38/1637 (2.3%)	7/472 (1.5%)	9/445 (2.0%)	6/318 (1.9%)	16/402 (4.0%)	0.027	0.023
Numbers of Mets' Components Mets						<0.001	<0.001
1 Mets component	933/1637 (57.0%)	328/472 (69.5%)	268/445 (60.2%)	158/318 (49.7%)	179/402 (44.5%)		
2 Mets components	509/1637 (31.1%)	105/472 (22.2%)	142/445 (31.9%)	108/318 (34.0%)	154/402 (38.3%)		
No Mets component	189/1637 (11.5%)	38/472 (8.1%)	32/445 (7.2%)	51/318 (16.0%)	68/402 (16.9%)		

Table 5. Simple and Multiple GEE Analyses, with RR (95% CI), of Serum ALT and AST Levels and Incidence of Mets and its components in Maleparticipants

Items	ALT			AST		
	Model 1 (crude)	Model 2	Model 3	Model 1 (crude)	Model 2	Model 3
Mets[a]						
Q1	1	1	1	1	1	1
Q2	**1.504 (1.178-1.919)**	**1.348 (1.041-1.745)**	1.114 (0.837-1.483)	**1.472 (1.172-1.849)**	**1.400 (1.101-1.781)**	1.268 (0.966-1.665)
Q3	**2.591 (2.051-3.275)**	**2.279 (1.774-2.928)**	**1.731 (1.315-2.279)**	**1.865 (1.478-2.354)**	**1.675 (1.308-2.146)**	**1.412 (1.065-1.873)**
Q4	**3.743 (2.949-4.750)**	**2.815 (2.120-3.738)**	**2.223 (1.639-3.016)**	**2.851 (2.255-3.604)**	**1.887 (1.439-2.474)**	**1.601 (1.188-2.158)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.002
Hypertension[b]						
Q1	1	1	1	1	1	1
Q2	**1.211 (1.060-1.383)**	1.144 (0.990-1.322)	1.036 (0.876-1.225)	**1.329 (1.164-1.518)**	**1.253 (1.085-1.446)**	**1.241 (1.050-1.467)**
Q3	**1.446 (1.255-1.666)**	**1.326 (1.134-1.551)**	1.097 (0.915-1.314)	**1.525 (1.324-1.756)**	**1.359 (1.165-1.586)**	**1.305 (1.094-1.558)**
Q4	**1.497 (1.282-1.749)**	**1.359 (1.122-1.646)**	1.172 (0.941-1.459)	**1.853 (1.591-2.157)**	**1.487 (1.252-1.767)**	**1.432 (1.179~1.738)**
P for trend	<0.001	<0.001	0.139	<0.001	<0.001	0.001
Hyperlipidemia[c]						
Q1	1	1	1	1	1	1
Q2	**1.785 (1.581-2.015)**	**1.604 (1.412-1.821)**	**1.445 (1.236-1.690)**	**1.418 (1.260-1.596)**	**1.382 (1.222-1.563)**	**1.302 (1.112-1.526)**
Q3	**2.676 (2.352-3.044)**	**2.079 (1.802-2.399)**	**1.799 (1.510-2.144)**	**1.657 (1.460-1.881)**	**1.415 (1.233-1.623)**	**1.272 (1.066~1.519)**
Q4	**4.504 (3.893-5.211)**	**2.576 (2.153-3.082)**	**2.291 (1.858-2.825)**	**2.647 (2.304-3.040)**	**1.590 (1.355-1.865)**	**1.401 (1.151-1.706)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.004
Obesity[d]						
Q1	1	1	1	1	1	1
Q2	**1.733 (1.531-1.961)**	**1.740 (1.525-1.986)**	**1.566 (1.344-1.825)**	**1.289 (1.146-1.450)**	**1.272 (1.124-1.439)**	**1.306 (1.128-1.513)**
Q3	**2.644 (2.313-3.022)**	**2.517 (2.178-2.909)**	**2.221 (1.884-2.617)**	**1.561 (1.376-1.770)**	**1.477 (1.292-1.689)**	**1.502 (1.285-1.755)**
Q4	**3.519 (3.039-4.075)**	**3.220 (2.712-3.823)**	**2.746 (2.261-3.336)**	**1.923 (1.674-2.210)**	**1.561 (1.334-1.828)**	**1.580 (1.322-1.889)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Hyperglycemia[e]						
Q1	1	1	1	1	1	1
Q2	0.988 (0.787-1.241)	0.956 (0.747-1.224)	0.758 (0.581-0.989)	**1.897 (1.380-2.607)**	**1.590 (1.159-2.180)**	1.276 (0.976-1.667)
Q3	1.070 (0.829-1.383)	1.096 (0.827-1.453)	0.840 (0.625-1.127)	**1.976 (1.503-2.597)**	**1.680 (1.230-2.294)**	**1.474 (1.148-1.892)**
Q4	1.249 (0.951-1.638)	1.224 (0.885-1.693)	1.132 (0.821-1.560)	**2.259 (1.665-3.063)**	**1.652 (1.227-2.223)**	**1.514 (1.207-1.898)**
P for trend	0.116	0.199	0.568	<0.001	<0.001	<0.001
Fatty liver[f]						
Q1	1	1	1	1	1	1
Q2	**2.995 (2.403-3.734)**	**3.059 (2.424-3.860)**	**2.614 (1.992-3.429)**	**1.438 (1.203-1.718)**	**1.406 (1.167-1.693)**	**1.484 (1.181-1.865)**
Q3	**5.715 (4.606-7.090)**	**5.817 (4.618-7.327)**	**4.602 (3.512-6.029)**	**2.247 (1.884-2.679)**	**2.202 (1.832-2.646)**	**2.211 (1.767-2.766)**
Q4	**12.241 (9.852-15.209)**	**12.551 (9.873-15.956)**	**9.787 (7.407-12.931)**	**3.968 (3.325-4.735)**	**3.294 (2.714-3.998)**	**3.382 (2.693-4.247)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note. Model 2 adjusted for age, GGT, smoking, and drinking; [a]model 3 adjusted for age, smoking, drinking, GGT, T-CH, TBIL, Cr, and WBC; [b]model 3 adjusted for [a]model 3 + hyperlipidemia, obesity, and hyperglycemia; [c]model 3 adjusted for [a]model 3 + hypertension, obesity, and hyperglycemia; [d]model 3 adjusted for [a]model 3 + hypertension, hyperlipidemia, and hyperglycemia; [e]model 3 adjusted for [a]model 3 + hypertension, hyperlipidemia, and obesity; [f]model 3 adjusted for [a]model 3 + hypertension, hyperlipidemia, obesity, and hyperglycemia.

parameters not included in the definition of Mets, such as Cr, WBC, TBIL, and CH (model 3). In model 3, the association was attenuated but was consistently significant. In female participants (Table 6), analysis of the association between altered serum ALT and AST levels and incidence of Mets by using models 2 and 3 did not require adjustment of smoking and drinking behavior because few female participants showed this behavior. Compared with respective lowest quartiles, multivariate adjusted RRs for high serum ALT and AST levels in the fourth quartile were 3.381 (1.761-6.493) and 1.567 (1.033-2.379), respectively.

Analysis of the association between ALT and AST levels and individual Mets component by using model 3 required adjustment of age, GGT, Cr, WBC, TBIL, T-CH, and 3 other Mets components; smoking and drinking were also adjusted in male participants. In both male and female participants, increasing ALT levels were positively correlated with hyperlipidemia and obesity in models 1, 2, and 3. Association between increasing ALT levels and hypertension was significant in models 1 and 2. Furthermore, adjustment of potential covariates showed that AST levels were positively correlated with all the Mets components in both male and female participants.

Analysis of the association between altered ALT and AST levels and fatty liver by using model 3 required adjustment of age, GGT, Cr, WBC, TBIL, T-CH, and four Mets components; smoking and drinking were also adjusted in male participants. Significant positive association was observed between serum ALT and AST levels and fatty liver. Moreover, the association between high ALT levels and fatty liver was much stronger than that between high AST level and fatty liver, particularly in male participants.

Association between serum ALT and AST levels and incidence of Mets was consistently observed among the following subgroups: participants with ALT<40 U/L at baseline, participants with AST<40 U/L at baseline, participants with BMI<25 kg/m^2 at baseline, and participants with non-fatty liver at baseline (Table 7).

Moreover, we divided the cohort into the following three subgroups according to the number of Mets components at baseline: participants with no Mets components at baseline, participants with one Mets component at baseline, and participants with two Mets components at baseline. Participants with two Mets components at baseline showed lower multivariate adjusted RRs of ALT and AST levels for Mets than participants with no or one Mets component.

DISCUSSION

By using large-scale health examination data involving repeated observations, our study showed that a longitudinal increase in serum ALT and AST levels was a biomarker for Mets even when the levels were in reference limits. As reported in previous cohort studies, increasing baseline ALT and AST levels were positively associated with the incidence of Mets[19-20]. In this dynamic cohort study involving the GEE model, use of increasing ALT and AST levels during follow-up and adjustment of increasing values of potential confounding factors showed that the incidence of Mets progressively increased with an increase in ALT and AST levels.

Unlike fixed cohorts studies where most participants have the same entry and follow-up times, entry and health examination frequency of participants were different in our dynamic cohort study. In the present study, all data of the first examination were set as baseline data and each follow-up year was counted from baseline. In previous cohort studies, associations were analyzed between baseline variables and targeted events at the end. However, in the present study, associations was analyzed by including time-varying variables and events from baseline to each follow-up year, which evaluated average treatment effects among several repeated observations between serum ALT and AST levels and incidence of Mets, with repeated observations analyzed using the GEE model.

In the recent decade, many studies have shown an association between serum ALT and AST levels and incidence of Mets and have stated that these levels are a biomarker for Mets, with serum ALT level being more sensitive as a biomarker of Mets than serum AST levels[13,21]. Hsieh MH found that the sensitivities of serum ALT and AST levels for Mets were 68.37% and 60.93%, respectively[11]. A study by Forlani used multivariate logistic regression after adjusting for age, gender, BMI, etc. to show that elevated AST levels were not associated with the incidence of Mets[13]. Villegas obtained similar results in studies involving middle-aged urban Chinese men[19].

In the present study, similar tendencies were observed in the association between ALT and AST levels and incidence of Mets in both male and female participants. This maybe because serum GGT,

Table 6. Simple and Multiple GEE Analyses, with RR (95% CI), of Serum ALT and AST levels and Incidence of Mets and its Components in Female Participants

Items	ALT			AST		
	Model 1 (crude)	Model 2	Model 3	Model 1 (crude)	Model 2	Model 3
Mets[a]						
Q1	1	1	1	1	1	1
Q2	1.636 (0.839-3.189)	1.626 (0.815-3.247)	1.738 (0.831-3.641)	1.132 (0.737-1.740)	1.132 (0.737-1.740)	0.972 (0.595-1.587)
Q3	**2.453 (1.351-4.455)**	**2.178 (1.165-4.072)**	1.921 (0.981-3.763)	**1.579 (1.065-2.339)**	**1.579 (1.065-2.339)**	1.319 (0.849-2.048)
Q4	**5.171 (2.909-9.193)**	**4.210 (2.288-7.745)**	**3.381 (1.761-6.493)**	**2.253 (1.562-3.248)**	**2.253 (1.562-3.248)**	**1.567 (1.033-2.379)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Hypertension[b]						
Q1	1	1	1	1	1	1
Q2	0.974 (0.778-1.221)	0.899 (0.702-1.151)	0.977 (0.737-1.294)	0.935 (0.762-1.146)	0.876 (0.708-1.084)	0.881 (0.681-1.139)
Q3	**1.278 (1.028-1.590)**	1.180 (0.928-1.499)	1.134 (0.865-1.487)	1.186 (0.979-1.437)	1.066 (0.874-1.301)	1.119 (0.881-1.422)
Q4	**1.438 (1.161-1.780)**	**1.340 (1.052-1.706)**	1.167 (0.886-1.536)	**1.451 (1.201-1.752)**	**1.244 (1.102-1.517)**	1.226 (0.965-1.557)
P for trend	<0.001	<0.002	0.452	<0.001	<0.001	0.002
Hyperlipidemia[c]						
Q1	1	1	1	1	1	1
Q2	1.197 (0.931-1.539)	1.173 (0.904-1.522)	1.212 (0.868-1.692)	1.131 (0.940-1.359)	1.151 (0.954-1.388)	1.109 (0.863-1.426)
Q3	**1.695 (1.338-2.147)**	**1.578 (1.236-2.014)**	**1.583 (1.167-2.148)**	**1.360 (1.140-1.622)**	**1.315 (1.098-1.575)**	1.175 (0.926-1.492)
Q4	**3.434 (2.728-4.322)**	**2.444 (1.908-3.130)**	**2.156 (1.588-2.928)**	**1.956 (1.652-2.317)**	**1.476 (1.233-1.766)**	**1.273 (1.002-1.617)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Obesity[d]						
Q1	1	1	1	1	1	1
Q2	1.220 (0.964-1.544)	1.217 (0.945-1.567)	1.258 (0.938-1.689)	1.086 (0.910-1.295)	1.065 (0.889-1.275)	1.044 (0.838-1.301)
Q3	**1.997 (1.592-2.506)**	**1.978 (1.553-2.520)**	**1.861 (1.403-2.467)**	**1.342 (1.132-1.592)**	**1.301 (1.093-1.549)**	**1.354 (1.095-1.673)**
Q4	**4.214 (3.365-5.278)**	**3.878 (3.033-4.958)**	**3.047 (2.299-4.040)**	**1.859 (1.572-2.198)**	**1.628 (1.365-1.942)**	**1.536 (1.245-1.894)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Hyperglycemia[e]						
Q1	1	1	1	1	1	1
Q2	0.858 (0.582-1.265)	0.744 (0.494-1.122)	0.943 (0.591-1.503)	**1.501 (1.011-2.230)**	**1.570 (1.132-2.178)**	**1.590 (1.159-2.180)**
Q3	0.996 (0.689-1.438)	0.855 (0.578-1.266)	0.884 (0.555-1.408)	**2.136 (1.413-3.230)**	**1.849 (1.334-2.562)**	**1.680 (1.230-2.294)**
Q4	1.033 (0.721-1.482)	0.945 (0.643-1.389)	0.848 (0.531-1.355)	**2.454 (1.652-3.647)**	**1.997 (1.462-2.728)**	**1.652 (1.227-2.223)**
P for trend	0.145	0.484	0.650	<0.001	<0.001	<0.001
Fatty liver[f]						
Q1	1	1	1	1	1	1
Q2	1.542 (0.980-2.426)	1.361 (0.852-2.173)	1.248 (0.668-2.333)	**1.511 (1.076-2.124)**	**1.498 (1.058-2.121)**	1.246 (0.826-1.882)
Q3	**2.920 (1.955-4.363)**	**2.502 (1.651-3.791)**	**2.185 (1.261-3.785)**	**2.111 (1.531-2.912)**	**2.064 (1.489-2.862)**	1.415 (0.963-2.079)
Q4	**6.847 (4.652-10.077)**	**5.222 (3.450-7.904)**	**3.501 (2.013-6.000)**	**4.549 (3.353-6.170)**	**4.184 (3.066-5.708)**	**2.664 (1.849-3.838)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note. Model 2 adjusted for age and GGT; [a]model 3 adjusted for age, GGT, T-CH, TBIL, Cr, and WBC; [b]model 3 adjusted for [a]model + hyperlipidemia, obesity, and hyperglycemia; [c]model 3 adjusted for [a]model 3 + hypertension, obesity, and hyperglycemia; [d]model 3 adjusted for [a]model 3 + hypertension, hyperlipidemia, and hyperglycemia; [e]model 3 adjusted for [a]model 3 + hypertension, hyperlipidemia, and obesity; [f]model 3 adjusted for [a]model 3 + hypertension, hyperlipidemia, obesity, and hyperglycemia.

Table 7. Multiple GEE Analysis, with RR (95% CI)[#], of Changes in Serum ALT and AST levels and Incidence of Mets in Subgroups

Items	ALT				AST			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mets								
No component[*] (*n*=1831)	1	0.617 (0.262-1.455)	1.790 (0.820-3.904)	**2.740 (2.185-6.336)**	1	1.453 (0.691-3.055)	0.951 (0.990-2.317)	**2.338 (1.967-5.655)**
1 component[*] (*n*=1544)	1	1.410 (0.783-2.538)	**2.745 (1.619-4.655)**	**3.471 (2.991-6.050)**	1	1.767 (1.051-2.973)	**2.952 (1.759-4.953)**	**2.843 (1.684-4.799)**
2 components[*] (*n*=1173)	1	0.904 (0.640-1.278)	1.146 (0.820-1.600)	**1.576 (1.097-2.264)**	1	1.049 (0.748-1.473)	1.168 (0.830-1.643)	1.356 (0.954-1.628)
ALT<40 U/L[*] (*n*=4008)	1	1.127 (0.840-0.952)	**1.608 (1.202-2.153)**	**2.811 (2.028-3.897)**	1	1.270 (0.944-1.709)	**1.505 (1.107-2.047)**	**1.816 (1.312-2.514)**
AST<40 U/L[*] (*n*=4379)	1	0.943 (0.765-1.164)	**1.601 (1.320-1.940)**	**2.338 (1.884-2.900)**	1	0.881 (0.727-1.068)	1.087 (0.896-1.318)	**1.387 (1.132-1.700)**
BMI<25 kg/m^{2}[*] (*n*=3129)	1	0.945 (0.652-1.368)	**1.739 (1.233-2.453)**	**2.166 (1.478-3.175)**	1	1.376 (0.952-1.989)	**1.697 (1.158-2.487)**	**1.672 (1.104-2.533)**
Nofatty liver[*] (*n*=4480)	1	0.881 (0.727-1.068)	1.087 (0.896-1.318)	**1.387 (1.132-1.700)**	1	1.269 (0.971-1.657)	**1.495 (1.135-1.968)**	**1.851 (1.394-2.458)**

Note. [#]Adjusted for age, smoking, drinking, GGT, T-CH, TBIL, Cr, and WBC. [*]*P* for trend, <0.01.

which is closely associated with Mets, was adjusted in the multivariate analysis performed in the present study but not in previous studies. Moreover, use of the GEE model allowed the analysis of repeated measurements of ALT and AST levels during follow-up, which might be more accurate for determining the actual association compared with that observed in other studies, which only included baseline serum ALT and AST levels.

The present study did not show a significant association of serum ALT levels with individual Mets components such as hypertension and hyperglycemia after adjusting for three other components, which was inconsistent with that observed in some previous studies[22-24]. Hypertension and hyperglycemia may be the final manifestations of complex metabolic disorders[25]. Moreover, hyperglycemia is caused by both insulin resistance and impaired pancreatic islet B cell function[26-27]. Therefore, no direct association may exist between serum ALT and AST levels and hypertension and hyperglycemia.

However, it is unclear how increased serum ALT and AST levels predict the development of Mets. One mechanism maybe the deregulation of normal amino acid metabolism in the liver, which may lead to liver fibrosis and Mets[28]. Elevated ALT and AST levels might reflect high hepatic transamination of amino acids and special compounds such as glutamate, which may pathologically cause hyperglycemia and type 2 diabetes mellitus (T2D)[29]. Another important common cause of elevated serum ALT and AST levels is NAFLD[30-31]. High ALT and AST levels suggest excessive lipid deposition in the liver even before the liver becomes fatty[31]. Insulin resistance is the sole link in the development of Mets[32-34] that can lead to increased hepatic gluconeogenesis, overproduction of TG-rich lipoproteins, and consequently NAFLD[35]. Therefore, ALT and AST levels may reflect more generalized insulin resistance and early stage of Mets before the occurrence of general metabolic disorders[21].

Positive correlation exists between ALT and AST levels and NAFLD, which may distort the association between ALT and AST levels and incidence of Mets. However, previous studies did not assess the effect on the presence of a fatty liver. Our study showed that the correlation between serum ALT and AST levels and incidence of Mets remained consistently significant in a dose-response manner in participants without a fatty liver, as determined by ultrasonography. Further, even when ALT and AST levels were in the reference ranges, high serum ALT and AST levels predicted increased incidence of Mets, which suggested that slightly increased ALT and AST levels should be looked upon with caution. Recent studies suggest that obesity is the initial state of Mets and that an increase in ALT and AST levels over time is caused by changes in BMI[11,36]. In our study, high ALT and AST levels were positively associated with the incidence of Mets even among participants with normal weight (BMI<25 kg/m^{2}). Therefore, individuals with normal weight who have in creased ALT and AST levels may have a high risk of

developing Mets.

Because Mets includes four components, individuals without Mets may have 0-2 components of Mets, reflecting different metabolic conditions. Therefore, when exploring the association between ALT and AST levels and incidence of Mets, it is essential to divide participants into subgroups based on the number of Mets components at baseline. In our study, stronger association was observed between ALT and AST levels and incidence of Mets in participants with no or 1 Mets component than in participants with 2 Mets components at baseline. However, the reason for the same is unclear. One explanation is that ALT and AST levels are biomarkers of the early stage of metabolic disorders. In participants with 2 Mets components, metabolic disorders were irreversibly settled, which weakened the association in these participants. Yun JE et al. showed that increased ALT levels were more closely associated with the risk of Mets in individuals aged <50 years than in individuals aged>50 years[37], which is partly consistent with our findings.

Some limitations of the present study should be noted. (1) Information obtained using the standard interviews was self-reported by the participants. Therefore, recalling bias may exist. (2) Because of the limited sample size, the study participants were not dichotomized according to gender during subgroup analysis. However, because of gender differences in the distribution of ALT and AST, quartiles of ALT and AST were divided separately in male and female participants in each subgroup. Moreover, in multivariate analysis, gender was adjusted in multiple GEE models. However, further studies involving large sample sizes are required for dichotomizing male and female participants. (3) We used the CDS definition of Mets with BMI instead of waist circumference. However, the CDS definition of Mets was formulated specifically for the Chinese population, and many studies have shown that BMI is as effective as waist circumference for diagnosing Mets[38].

CONCLUSION

East Asians have higher risk of Mets and cardiovascular disease than westerners[39]. Therefore, it is important to determine early biomarkers for predicting and diagnosing Mets in the Chinese population. The present dynamic cohort study performed in Dongying City, China, offered solid evidence that elevated serum ALT and AST levels were biomarkers of Mets. Although Receiver Operating Characteristic (ROC) curves did not show high sensitivity and specificity of ALT and AST levels (data not shown), further studies are warranted to show increased sensitivity and specificity of ALT and AST levels by performing combined tests with other Mets-related biomarkers such as uric acid and TBIL.

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AUTHOR CONTRIBUTION STATEMENT

SW and JX designed the study and directed its implementation. QC performed clinical exam and collected data. PZ and LC analyzed the data. XC provided scientific comments and advice. JX wrote the manuscript. All authors read and approved the final manuscript.

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