The relationship between 25-hydroxyvitamin D concentration and liver enzymes in healthy adults: A Cross-sectional Study

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Research article

Keywords: Vitamin D, Liver function, ALT, GGT, ALP

Posted Date: January 24th, 2020

DOI: https://doi.org/10.21203/rs.2.21858/v1

Abstract

Background: Studies have shown that serum 25-hydroxyvitamin D (25(OH)D), a product of exogenous vitamin D, plays an influential role in calcium and phosphorus balance, anti-inflammation, and cardiovascular protection. There were long-standing interests in the potential benefits of vitamin D for preventing liver diseases. Investigations showed that 25(OH)D was increased in adolescents with abnormal liver function. Yet data about the relationship of 25(OH)D concentration and liver enzymes from prospective cross-sectional study was limited. The present study is undertaken to examine whether serum 25-hydroxyvitamin D and alanine aminotransferase (ALT) γglutamyl transferase (GGT) and alkaline phosphatase (ALP) were closely related.

Methods: The cross-sectional study of 368 healthy volunteers with no history of liver diseases was used to examine risk factors. The associations between ALT, G and ALP and 25(OH)D were assessed by Pearson correlation and Spearman correlation, respectively. Linear regression analysis was carried out in different models with ALT, GGT and ALP as dependent variables.

Results: The results found no significant difference between ALT and ALP in different vitamin D groups (25(OH)D < 25 nmol/L，25-50 nmol/L and > 50 nmol/L) (Kruskal-Wallis test, all $p > 0.05$). Multiple linear regression analysis revealed that there were no significant association between ALT, GGT and ALP levels and 25(OH)D concentration, respectively, after adjusting covariates including age, BMI, sex, BuN, Cr, UA, AST, Ghb, ALB, WBC, cholesterol, HDL, LDL, cholesterol, and total protein. (All $p > 0.1$).

Conclusion: This study suggested that there was no association between the 25(OH)D concentration and the levels of ALT, GGT or ALP in normal population.

Background

Vitamin D originates from skin synthesis as a result of exposure to sunlight in vivo, supplementary and dietary vitamin D intake in vivo[1]. It is a group of liposoluble steroid derivatives, responsible for maintaining the strength of bones. In addition, vitamin D is able to reduce the risk of heart diseases, diabetes, breast cancer[2]. As we all know, suboptimal 25-hydroxyvitamin D3 is produced by exogenous vitamin D through liver hydroxylation, which can be used as a biomarker of vitamin D levels owing to its long-term stable levels[3]. Farnik and colleagues have shown that vitamin D not only maintains the balance of calcium and phosphorus, but also regulates immune system, anti-inflammation, anti-fibrosis, and cardiovascular protection function[4]. Recently, scientists confirmed that serum 25(OH)D levels were beneficial to clinical prevention of chronic hepatitis B[4]. Low serum 25(OH)D levels may lead to chronic hepatitis B infection. With deep exploration about new activity of vitamin D, it draws more attention from scientists[5].

The correlation between non-alcoholic fatty liver disease (NAFLD)and vitamin D deficiency was reported by Jeon et al. The results demonstrated that liver enzymes can be used as biomarkers for NAFLD of metabolic syndrome[6]. Eliades et al. found that decreased serum 25(OH)D concentration in NAFLD

patients by meta-analysis of 17 studies, indicating that vitamin D mayexert efferts in the development of NAFLD[6]. One study showed that vitamin D could play a positive part on NAFLD and NAFLD-related parameters, if well administered for medium–long periods[7]. However, current studies regarding the association of liver enzymes and 25(OH)D concentration remain discrepant. Naderpoor et al. observed that liver enzymes were affected by vitamin D supplementation through 54 persons in 16 weeks. Consequently, in adults without a history of liver disease, 25 (OH) D concentration was unlinked to liver enzymes. Vitamin D supplementation did not affect serum levels of liver enzymes in people with vitamin D deficiency or overweight [8]. However, Bahreynian et al. found higher rates of vitamin D deficiency were observed among individuals with high levels of liver enzymes. Recent study has showed that NAFLD patients have decreased serum 25(OH)D concentration, and vitamin D may exert efferts in the development of NAFLD[9]. To test the relationship between liver enemies and 25 (OH) D, detailed investigations were undertaken to examine their relationship in healthy individuals.

Methods

Study Design And Participants

This study recruited 368 healthy volunteers (males and females) without the history of liver diseases from the province of Anhui, China. Participants were recruited if the following criteria were met: ranged from 26 to 86 years, weight remained stable over the past 12 months (no weight change > 5 kg), no plans to lose weight, change diet or physical activity during the trial, and without comorbidities.The participants were required to no vitamin D supplements for at least three months prior to the recruitment of this study. Data was obtained from the ethical committee of Anhui Medical University (Protocol ID: 20170248) and all participants received written informed consent.

Anthropometric Measurements

Medical screening and examination were performed in the all participant(n = 368),including body weight, height, and blood pressure of the participants. Body mass index (BMI) was measured as weight (kg) / height squared (m^2). Total body dual energy X-ray absorptiometry (DEXA) (Lunar Radiation Corp., Madison, WI, USA) were used to assess the body health condition.

Metabolic Measurements

Average systolic and diastolic blood pressures were derived from three measurements by an automated sphygmomanometer (M6 Automatic BP monitor, Omron, Japan) after a break of at least five minutes.

Fasting venous blood samples were analyzed for 25 (OH) D concentration (direct competitive chemiluminescent immunoassays, DiaSorin Inc., MN, USA), inter- and intra-analysis coefficient of variation (< 10% and < 4%). Glucose (glucose oxidase assay, YSI 2300 Stat, YSI Inc., OH, USA), insulin, kidney and liver tests, lipid assay (all using commercial enzymatic immunoassays, Beckman Coulter, Australia) and whole blood cell count (Beckman Coulter LH750) were contained in test contents.Insulin

sensitivity was measured with hyperinsulinemia-normal glucose clamp as our protocol, including initial intravenous injection of insulin pills (9 mU/kg), followed by continuous infusion of insulin at a rate of 40 mU/m2/min for at least 120 minutes.

Meanwhile, blood glucose were stabilized at about 5 millimole/liter through the adjustment off glucose infusion. According to the last 30 minutes of the clamp and the stable glucose infusion rate, the total insulin stimulation glucose treatment rate (M value) was calculated.

Statistical analysis

The baseline characteristics of the participants were presented as the mean ± standard deviation (SD) of the normal distribution variable and the median [interquartile range (IQR)] of the non-normal distribution variable. The normality of the distribution was assessed using a frequency histogram and a visual inspection of the Shapiro-Wilk test. Logarithmic transformation values were usconducted ed to approximate a normal distribution when required by parametric testing.

Results

The study population (n = 368) included males and females aged 26–86 years. There were no significant differences in age, fasting FBG, AST, Ghb, cholesterol, HDL, LDL, triglycerides, total protein, ALB, WBC, ALP and 25(OH)D (all $p > 0.05$). Male participants had a lower BMI ($p = 0.01$), higher diastolic blood pressure ($p = 0.03$), higher urea nitrogen (BuN) ($p < 0.001$), Cr ($p = 0.02$), uric acid (UA) ($p = 0.01$), ALT ($p = 0.03$). and GGT ($p = 0.01$) Baseline characteristics of participants were summarized in Table 1.

Table 1

Baseline characteristic of participants in the cross-sectional study.

Variable	All participants	Males	Female	p-value
[a]Age (year)	49.00 [12.00]	48.00 [11.75]	49.00 [12.00]	0.76
BMI (kg/m^2)	24.61±3.16	24.61±3.16	25.27±3.38	0.01
[a]SBP (mmHg)	119.0 [14.0]	123.0 [16.0]	118.0 [13.0]	0.12
[a]DBP (mmHg)	75.00 [11.00]	79.00 [12.00]	73.00 [10.00]	0.03
[a]GLU (mmol/L)	5.28 [0.84]	5.36 [0.88]	5.15 [0.66]	0.59
[a]BUN (mmol/L)	5.37 [1.75]	5.59 [1.50]	4.85 [1.60]	< 0.001
[a]Creatinine (umol/L)	70.00 [21.00]	76.00 [13.00]	53.00 [16.00]	0.02
UA (umol/L)	332.4±86.9	366.5±77.8	265.2±61.0	0.01
[a]AST (U/L)	21.00 [9.00]	21.00 [9.00]	19.50 [7.75]	0.06
[a]HbA1C (%)	5.50 [0.55]	5.50 [0.55]	5.50 [0.50]	0.29
HDL (mmol/L)	1.27 [0.45]	1.21 [0.35]	1.32 [0.52]	0.06
[a]LDL (mmol/L)	2.93 [1.05]	3.09 [1.28]	2.84 [1.06]	0.15
[a]Triglyceride (mmol/L)	1.38 [1.10]	1.93 [1.36]	1.11 [1.03]	0.06
TP (g/L)	74.70±3.80	74.49±3.69	75.12±3.99	0.71
Alb (g/L)	47.86±2.67	44.52±3.94	49.18±2.15	0.55
[a]WBC (10^9/L)	5.92 [1.90]	5.99 [1.26]	5.63 [1.47]	0.39
[a]GGT (U/L)	24.00 [27.75]	25.50 [16.75]	15.5 [12.75]	0.01
[a]ALT (U/L)	21.00 [18.75]	25.00 [20.75]	15.00 [12.75]	0.03
[a]ALP (U/L)	74.00 [25.00]	75.00 [24.00]	67.00 [24.00]	0.06
[a]25(OH)D (nmol/L)	22.85 [18.25]	22.65 [19.35]	23.95 [15.65]	0.83

ALT: alanine aminotransferase; ALP: alkaline phosphatase; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GGT: γ-glutamyl transferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; 25(OH)D: 25-hydroxyvitamin D.

[a] Data are presented as median [IQR] due to non-normal distribution

The bivariate correlations of ALT, GGT and ALP was presented in Table 2.

Table 2
Correlations of 25(OH)D, anthropometric, metabolic and inflammatory markers withGGT, ALT and ALP.

	GGT r (p-value)	ALT r (p-value)	ALP r (p-value)
25(OH)D (nmol/L)	0.036 (0.489)	-0.038 (0.466)	0.026 (0.623)
Age (year)	0.042 (0.039)	-0.156 (0.218)	0.047 (0.122)
BMI (kg/m^2)	0.128 (0.041)	-0.057 (0.233)	0.031 (0.059)
SBP (mmHg)	0.063 (0.051)	0.103 (0.154)	0.164 (0.201)
DBP (mmHg)	0.131 (0.043)	-0.097 (0.058)	0.212 (0.049)
GLU (mmol/L)	0.122 (0.031)	0.631 (0.007)	0.245 (0.010)
BUN (mmol/L)	0. 283 (0.242)	0.156 (0.214)	0.334 (0.257)
Creatinine (umol/L)	0.327 (0.839)	0.324 (0.127)	0.442 (0.041)
UA (umol/L)	0. 083 (0.443)	0.051 (0. 147)	0.304 (0.759)
AST (U/L)	0.029 (0.334)	0.024 (0.165)	0.543 (0.148)
HbA1C (%)	0. 423 (0.047)	0.068 (0. 205)	0.121 (0.032)
HDL (mmol/L)	0.214 (0.326)	0.540 (0.005)	0.129 (0.504)
LDL (mmol/L)	0.229 (0.235)	0.115 (0.608)	-0.045 (0.123)
Triglyceride (mmol/L)	0. 255 (0.011)	0.129 (0. 094)	0.216 (0.026)
TP (g/L)	0.034 (0.059)	0.128 (0.031)	0.112 (0.066)
Alb (g/L)	0. 133 (0.061)	0.072 (0. 147)	0.056 (0.043)
WBC (10^9/L)	0.058 (0.129)	0.320 (0.071)	0.132 (0.095)
GGT (U/L)		0.322 (< 0.001)	0.320 (< 0.001)
ALT (U/L)	0.322 (< 0.001)		0.166 (0.001)
ALP (U/L)	0.320 (< 0.001)	0.166 (0.001)	

ALT: alanine aminotransferase; ALP: alkaline phosphatase; BMI: body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GGT: γ-glutamyl transferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; 25(OH)D: 25-hydroxyvitamin D.

No significant correlation between 25(OH)D and any liver enzyme levels were observed (all $p > 0.05$). GGT was positively related to age and BMI ($p = 0.039$ and 0.041, respectively).

ALP was positively correlated with diastolic blood pressure ($p < 0.05$) and GGT was also positively related to diastolic blood pressure ($p = 0.045$).The three liver enzymes were positively related to each other and to FBG (all $p < 0.05$). However, there were no correlations between any liver enzyme levels and BuN, the same with UA (all $p > 0.05$). There was no relationship between the three enzymes and the lipid profile (all $p > 0.05$).

Lipid profile and AST were not associated with any liver enzymes (all $p > 0.05$). GGT and ALP were positively related to Ghb ($p = 0.047$ and 0.032 respectively).There was a positive relationship between ALT and HDL($p = 0.047$). GGT and ALP were positively associated with triglycerides ($p < 0.05$). However, three liver enzymes had no correlations with the levels of ALB and WBC (all $p > 0.05$).

There were no significant associations of GGT, ALT, ALP levels to 25(OH)D concentration after adjustments for covariates including age, BMI, sex, BuN, Cr, UA,AST, Ghb, cholesterol, HDL, LDL, and total protein, ALB and WBC in multiple linear regression analysis (Table 3a–3c) (all $p > 0.1$).In these models, GGT was associated with sex ($p < 0.01$) (Table 3a). ALT was related to sex and BuN (all $p < 0.05$) (Table 3b). ALP was associated with AST and triglycerides (all $p < 0.05$).

Table 3a.

Multiple linear regression analyses for GGT.

Dependent variable	Independent variable	Model 1		Model 2	
		β	p-value	β	p-value
GGT	25(OH)D	0.23	0.12	0.07	0.45
	Age	-0.02	0.57	0.31	0.15
	BMI	0.03	0.45	0.18	0.06
	Sex	0.39	< 0.01	0.27	0.44
	SBP				
	DBP				
	GLU			0.07	0.06
	BUN	0.16	0.25	0.29	0.37
	Creatinine	-0.07	0.44	0.31	0.45
	UA	0.31	0.15	0.18	0.19
	AST	0.19	0.07	0.27	0.56
	HbA1C	0.04	0.05	0.25	0.20
	HDL	0.28	0.27	0.13	0.55
	LDL	0.37	0.42	0.24	0.05
	Triglyceride	0.15	0.29		
	TP	0.07	0.53	0.22	0.38
	Alb	0.24	0.10	0.21	0.41
	WBC	0.11	0.61	0.39	0.57
	R^2 (p-value)	0.46	< 0.01	0.45	< 0.01

Model 1: adjusted for age, sex, BMI, SBP, DBP, BUN, Creatinine, UA, AST, HbA1C, HDL, LDL, Triglyceride, TP, Alb, WBC.

Model 2 adjusted for age, sex, BMI, SBP, DBP, GLU, BUN, Creatinine, UA, AST, HbA1C, HDL, LDL, TP, Alb, WBC.

Table 3b.

Multiple linear regression analyses for ALT.

Dependent variable	Independent variable	Model 1		Model 2	
		β	p-value	β	p-value
ALT	25(OH)D	0.14	0.26	0.08	0.34
	Age	0.05	0.39	0.22	0.17
	BMI	0.16	0.41	0.35	0.19
	Sex	0.34	0.02	-0.07	0.31
	SBP	0.07	0.23	0.14	0.07
	DBP	-0.14	0.12	-0.12	0.26
	GLU			0.18	0.05
	BUN	0.17	0.02	0.13	0.30
	Creatinine	0.29	0.38	0.26	0.14
	UA	0.28	0.43	-0.02	0.29
	AST	0.17	0.06	0.03	0.57
	HbA1C	0.09	0.45	0.38	0.11
	HDL	0.31	0.15		
	LDL	0.18	0.06	0.27	0.18
	Triglyceride	0.27	0.34	0.24	0.03
	TP	-0.02	0.13	0.39	0.21
	Alb	0.42	0.15	0.46	0.35
	WBC	0.33	0.27	0.48	0.23
	R^2 (p-value)	0.31	< 0.01	0.16	< 0.01
Model 1: adjusted for age, sex, BMI, SBP, DBP, BUN, Creatinine, UA, AST, HbA1C, HDL, LDL, Triglyceride, TP, Alb, WBC.					
Model 2 Model 1: adjusted for age, sex, BMI, SBP, DBP, GLU, BUN, Creatinine, UA, AST, HbA1C, LDL, Triglyceride, TP, Alb, WBC.					

Table 3c.Multiple linear regression analyses for ALP.

Dependent variable	Independent variable	Model 1		Model 2	
		β	p-value	β	p-value
ALP	25(OH)D	0.31	0.34	0.21	0.23
	Age	0.07	0.25	-0.09	0.21
	BMI	0.35	0.23	0.16	0.39
	Sex	0.12	0.56	0.17	0.32
	SBP	0.21	0.09	0.22	0.17
	DBP	-0.15	0.06	-0.09	0.28
	GLU			0.19	0.31
	BUN	0.17	0.12	0.16	0.28
	Creatinine	0.24	0.38	0.29	0.37
	UA	0.23	0.06	0.18	0.06
	AST	0.17	0.03	0.13	0.34
	HbA1C	-0.09	0.47	0.26	0.17
	HDL	0.21	0.39		
	LDL	0.15	0.08	0.55	0.19
	Triglyceride	0.36	0.32	0.24	0.03
	TP	-0.02	0.16	-0.04	0.23
	Alb	0.42	0.15	0.46	0.56
	WBC	0.33	0.27	0.42	0.22
	R^2 (p-value)	0.24	<0.01	0.19	<0.01

Model 1: adjusted for age, sex, BMI, SBP, DBP, BUN, Creatinine, UA, AST, HbA1C, HDL, LDL, Triglyceride, TP, Alb, WBC.

Model 2: adjusted for age, sex, BMI, SBP, DBP, GLU, BUN, Creatinine, UA, AST, HbA1C, HDL, LDL, TP, Alb, WBC.

When classified by 25 (OH) D concentration, the 25 (OH) D of 6 participants was > 50 nmol/L, the 25 (OH) D of 159 participants was 25–50 nmol/L, and the 25 (OH) D of 203 participants was less than 25 nmol/L.No significant differences were observed in GGT, ALT and ALP according to the categories of vitamin D concentration (Kruskal-Wallis test, all p > 0.05).

Discussion

The cross-sectional study, which explored the relationship between 25 (OH) D concentration and liver enzymes, showed no association with healthy adults before and after adjustment for potential confounding factors, including age, gender, obesity markers, insulin sensitivity, lipids and inflammation.

Liver enzymes were associated with the metabolic syndrome (MS) factors including FBG and triglycerides. Additionally, ALT, GGT and ALP were positively interacted to each other. Similarly, Ballestri et al. demonstrated that liver histology changes could be predicted significantly using ALT, AST, homeostasis model of assessment-insulin resistance (HOMA-IR), serum uric acid (SUA), MS, total cholesterol (TCH) and serum iron[10].

Vitamin D can be acquired from the diet, but it is mainly produced by endogenous sun exposure[11]. Transported to the liver, vitamin D is hydroxylated to 25(OH)D by monooxygenase system in microsome. It is generally accepted that serum 25(OH)D concentration could be used to assess status of vitamin D and musculoskeletal growth. What's more, nutritional guidelines of vitamin D should be based on effects of vitamin D[12]. It is well known that vitamin D is beneficial to calcium and bone metabolism. Studies have confirmed that vitamin D has a series of physiological functions and its deficiency can lead to many diseases. Recent studies have shown that it regulates adaptive immune responses to various inflammatory and autoimmune diseases. Both vitamin D hydroxylase and vitamin D receptor (VDR) were expressed in immune cells, which lay a foundation for vitamin D to play its role in inflammatory diseases. 25(OH)D acts as a ligand for the VDR and participates in diverse physiological processes[13]. Furthermore, the elevation of ALT, GGT and ALP were closely related to liver fat deposition and were considered to be an indicator of liver injury [14–17].

As mentioned earlier, ALT can serve as an index of hepatocyte death and indices of liver injury[15, 18]. GGT was involved in extracellular catabolic metabolism of the antioxidant glutathione and was considered to be a marker of oxidative stress and subclinical inflammation [16]. ALP was responsible for hydrolysis of phosphate esters. An up to triple improvement of ALP was common to see in hepatocellular diseases, accompanied with elevated aminotransferases[19]. At the same time, ALP was significantly increased in cholestatic hepatobiliary diseases as well, for instance, primary biliary intrahepatic cholestasis[13]. However, the real fact was that AST was a less specific index of liver injury on account of wide secretion from other organs and cells, such as the heart, skeletal muscle, kidney, pancreas, lung, leukocyte, and erythrocyte[18–20].

Similar to our findings, three articles were presented to support our conclusion. The first study from the third National Health and Nutrition Examination Survey (NHANES III) demonstrated that there was no relationship between serum ALT levels and25(OH)D concentration. The result of this study was consistent with previous irrelevance outcome between ALT and 25(OH)D concentration[15]. However, the study showed that the lower quartile of 25(OH)D had a higher prevalence of unexplained ALT, individuals with elevated ALT levels (n = 308) had a lower concentration of 25(OH)D, compared to BMI-matched controls (n = 976). Notably, individuals with different comorbidities such as diabetes and hypertension

were included, and drug use was not adjusted, which may have affected their results. Meanwhile, the second one included 654 individuals with diabetes risk factors (aged ≥ 30 years) whose 25(OH)D concentration had a negative association with ALT after adjusting for BMI, waist circumference, and lipids [16]. On the contrary the third one using NHANES III data for 12,155 participants with normal ALT levels, showed a positive correlation between 25(OH)D concentration and ALT levels, after adjusting for confounding factors, such as gender, race, BMI, diabetes, high blood pressure, smoking and drinking history. One thing to be noted was that all individuals with serum ALT levels > 39 U/L were excluded in their study. However, our study did not require ALT levels and everyone included. Therefore, their findings were not comparable to other conclusions, as higher ALT levels may be related to liver damage and severe comorbidities.

There were some limitations in our study. Firstly, due to the cross-sectional design of our study, we can't conclude cause and effect relationships and evaluate the impact of vitamin D status over time. Secondly, vitamin D concentration is measured for one time. However, a previous study declared that a single measurement of serum 25(OH)D had reasonable validity over a 5-year period[21]. Multiple measurements of 25(OH)D would estimate the vitamin D status better and reduce the extent of non-differential measurement errors. Thirdly, the status of vitamin D may be confusing because vitamin D concentrations may generally be influenced by a different lifestyles[22, 23]. In our model, we have adjusted other determinants. However, possible residual confusion may not be ruled out. Finally, adverse effects of vitamin D use were not discussed in this article. More deep research for liver injury should be carried out to re-evaluate and determine relationships between 25-hydroxyvitamin D concentration and liver enzymes, using larger sample sizes, longer durations and more sensitive screening tools.

Conclusion

In summary, finding from some but not all cross-sectional studies suggested a relationship between 25(OH)D concentration and liver enzymes, which were within the normal ranges. The reason why our results were not related to the 25(OH)D concentration and ALT levels were that our sample size was large and the participants were older (our sample median age = 49). In our study performed in Chinese population within 368 healthy drug-naïve individuals,. the results revealed ALT, GGT and ALP levels remained unrelated to 25(OH)D concentration

Abbreviations

ALP
alkaline phosphatase; ALT:alanine aminotransferase; BMI:Body mass index;
FBG
fasting blood-glucose; Ghb:glycated hemoglobin; GGT:glutamyl transferase;
NAFLD
non-alcoholic fatty liver disease; NHANES III:the third National Health and Nutrition Examination Survey;
WBC:white blood cell

Declarations

Ethics approval and consent to participate

The ethical approval was obtained from the Ethical Committee of Anhui Medical University (Protocol ID: 20170248). All patients and healthy persons included in this study provided written informed consent. The clinical trial information sheath was given to all patients that include the objectives, methodology and purpose of the study using a simple layman term.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The National Natural Science Foundation of China (Nos. 81700522, 81470003), from the National Natural Science Foundation of China, supports the design of the study.

The Provincial Natural Science Research Project of Colleges and Universities of Anhui Province (No. KJ2016A348), from the Education Department of Anhui, China, supports the collection of data.

The fund of Anhui medical university doctoral start research (No.0601067101), from the Anhui Medical University, China, supports the analysis of data.

2017 public welfare technology application research linkage project of Anhui province (No.1704f0804019), from Anhui Province Science and Technology Department, China, supports the analysis of data.

Humanities and Social Science Research Project of Colleges and Universities of Anhui Province (No. SK2016A0482), from Anhui Province Science and Technology Department, China, supports the interpretation of data.

Natural Science Foundation of Anhui Province(1808085MH235), from the Education Department of Anhui, China, supports the writing of manuscript.

Funding bodies did not have a role in study design, or collection, analysis and interpretation of data, or manuscript writing.

Authors' contributions

TX and HH designed the study. JW, LL1 and LL2 participated in the collecting and analyzing of the data. QY and PL finished the manuscript. JL revised and edited the manuscript. YL and SC reviewed the manuscript. All authors approved the final version of the manuscript for publication.

Acknowledgments

Not applicable.

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