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Original Article

Predictive value of vitamin A and E levels in pre-eclampsia and postpartum kidney injury

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Abstract: Objective: This research aimed to explore the predictive value of levels of vitamin A and E in pre-eclampsia and postpartum kidney injury. Methods: A total of 106 pregnant women with severe pre-eclampsia diagnosed in our hospital from May 2015 to December 2018 were selected as the research subjects. There from, 75 pregnant women with severe pre-eclampsia were enrolled into the severe PE group (SPE) and 31 with acute kidney injury were divided into the severe PE and AKI group (SPE and AKI). Serum vitamin A and E content was determined by high-performance liquid chromatography (HPLC), and the correlation between vitamins A and E and disease was analyzed. The expression levels of kidney injury markers in both groups were detected, and the correlation between markers and vitamin A and E levels was analyzed. Results: The expression level of vitamins A and E decreased in the pre-eclampsia and postpartum kidney injury, and it was negatively correlated with disease severity. The expression of the two decreased further in the severe pre-eclampsia patients with kidney injury. In addition, the expression of kidney injury markers in the severe pre-eclampsia patients with postpartum kidney injury was higher than that in severe pre-eclampsia patients, and it was negatively correlated with vitamin A and E levels. Conclusion: Vitamins A and E are expressed in low levels in pre-eclampsia and postpartum kidney injury, and the latter has a higher sensitivity and specificity than the former. It is negatively correlated with kidney injury markers KIM-1, NGAL, UA and Scr, which can be used as a physical and chemical indexes for clinical prediction.

Keywords: Vitamins A and E, pre-eclampsia and postpartum kidney injury, kidney injury molecule 1, uric acid, neutrophil gelatinase-associated lipocalin, serum creatinine concentration

Introduction

Pre-eclampsia (PE) is a serious complication of pregnancy, affecting 5-8% of all pregnancies [1]. It can increase the morbidity and mortality of fetuses and pregnant women, especially in developing countries. It has harmful effects on several important organs, including the kidney, liver, brain and lung [2]. It is characterized by hypertension and proteinuria after the 20th week of pregnancy, which leads to neonatal morbidity and perinatal death. It is also one of the five major causes of maternal mortality in developed countries [3, 4].

PE pathogenesis is considered to be: incomplete infiltration of trophoblasts of the uterine spiral artery that leads to placental ischemia, which finally releases inflammatory factors, immune cell activation and endothelial dysfunction [5]. Besides, it is also related to oxidative stress (OS) [6]; because pregnancy will increase OS, it results in large circulating reactive oxygen species (ROS) and reactive nitrogen species (RNS) increase [7]. Therefore, enhancing antioxidant capacity is the way to overcome OS during pregnancy. Vitamin E is a hydrophobic antioxidant, while vitamin A is an essential fat-soluble micronutrient, which has the highest antioxidant potential among all vitamins [8, 9]. What's more, both vitamins A and E are essential micronutrients, which play a vital role in maternal health and fetal development [10]. Some studies have shown that the levels of vitamin A, C and E are all low in PE, and found that vitamin E level is negatively correlated with blood pressure [11, 12]. In addition, some studies have shown that supplementation of omega-3 fatty acids and vitamin E in PE pregnant women can relieve illness [13]. PE is a common cause of acute kidney injury (AKI) in low- and middle-income countries. PR-AKI is a

serious obstetric complication, which may have devastating effects on mothers, fetuses and newborns. Recently, the morbidity of PR-AKI has increased and it is related to gestational hypertension [14]. The AKI severity depends on the increase of serum creatinine (Scr) level or the decrease of urine output [15]. For a long time, uric acid may induce slight kidney damage, which is the inducing factor of AKI [16]; and urine biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) can also be used for early AKI diagnosis [17]. Other studies have shown that serum vitamin B12 level is negatively correlated with urine markers, and electrolytes in the urine, and kidney injury molecules in children lacking B12 also increase [18]. Now, the decrease of vitamin E in preeclampsia has been found more frequently, which may be a compensation mechanism to deal with the increased oxidative stress. Studies have shown that vitamin D supplementation during pregnancy can help reduce the incidence of pregnancy-induced hypertension/preeclampsia, and vitamin D (25OHD) deficiency < 10 ng/ml is related to AKI severity [19-21]. Therefore, we suspect that vitamin level is related to pre-eclampsia and postpartum kidney injury.

In order to make better analysis about PE on the basis of previous scholars, this study measured the levels of vitamin A and E in pregnant women, and evaluated the predictive value of the two in PE and their influence on postpartum kidney injury. We hope to improve the clinical data available for diagnosing and treating preeclampsia and postpartum kidney injury.

Materials and methods

Subjects of research

A total of 106 pregnant women with severe PE diagnosed in the Civil Aviation General Hospital from May 2015 to December 2018 were selected as the research subjects. Among them, 75 pregnant women with severe PE were selected as the severe PE group (SPE), being (28.1±3.5) years old on average; and another 31 women with AKI were treated as the severe PE and AKI group (SPE and AKI), being (28.9±4.1) years old on average. Inclusion criteria were as follows: severe PE: blood pressure and urinary protein continued to rise, and maternal organ dysfunction or fetal complications occurred. Any of the following adverse conditions could be used to diagnosed severe PE: (1) blood pressure went up steadily: systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg; (2) proteinuria ≥ 2 g/24 h or random proteinuria ≥ (+++); (3) persistent headache or visual disturbance or other cranial nerve symptoms; (4) persistent epigastric pain, sub-capsular hematoma of the liver or liver rupture; (5) abnormal liver function: elevated ALT or AST levels of liver enzymes; (6) abnormal renal function: oliguria (urine volume < 400 ml in 24 h or < 17 ml per hour) or Scr > 106 μmol/L; (7) hypoalbuminemia with pleural effusion or ascites; (8) abnormal blood system indicators: platelets decreased continuously and were lower than 100×10^9/L; intravascular hemolysis, anemia, jaundice or elevated blood LDH; (9) heart failure, pulmonary edema; (10) fetal growth restriction (FGR) or oligohydramnios; AKI: Scr increased ≥ 26.4 μmol/L or basal Scr concentration ≥ 1.5 times; without chronic heart, liver and kidney insufficiency, hypertension, diabetes and thyroid diseases. Exclusion criteria were as follows: hypertension, systemic lupus erythematosus, rheumatoid and other rheumatic immune diseases, diabetes and other endocrine diseases before pregnancy; medical history of tumor, combination, etc. This experiment was approved by the hospital ethics committee, and the study subjects signed an informed consent form.

Detection methods

Routine test included: blood and urine, liver and kidney function; SBP and DBP routine measurement.

Vitamin level test: the levels of vitamin A and E in the blood of pregnant women in both groups were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). In the same morning on an empty stomach, 3-5 mL venous blood was collected from the arm of pregnant women without anticoagulation and then centrifuged 10-15 min at 3000 r/min. The levels of vitamin A and E were quantitatively determined by agilent LC1100 liquid chromatograph.

Renal damage markers test: 4 mL urine from the middle part of the patient in the morning was collected and then centrifuged 10 min at

Table 1. General data

Factor	SPE (n=75)	SPE and AKI (n=31)	χ^2/t	P
Age	28.1±3.5	28.9±4.1	1.017	0.3114
BMI (kg/m^2)	24.28±2.68	24.63±2.27	0.638	0.5247
Gestational week at delivery	38.9±1.0	37.8±1.1	5.002	< 0.001
History of smoking			0.118	0.7314
Yes	9	3		
No	66	28		
History of family			1.009	0.3151
Yes	7	5		
No	68	26		
Blood pressure				
Diastolic blood pressure	96.54±4.32	99.15±3.29	3.018	0.0032
Systolic blood pressure	146.05±8.80	165.18±4.82	11.396	< 0.001
Urine protein (g/24 h)	1.61±0.53	7.32±4.33	11.292	< 0.001
AST (U/L)	23.16±10.86	40.12±10.52	7.380	< 0.001
ALT (U/L)	13.5±9.23	45.1±11.62	14.832	< 0.001
β2-microglobulin (mg/L)	3.54±0.73	3.92±0.81	2.360	0.0201
eGFR	93.22±21.01	73.23±11.21	5.002	< 0.001

4°C, 2000 r·min; finally, the supernatant was collected.

The reagents KIM-1 and NGAL were purchased from R&D Systems and detected by ELISA, and the results were determined by Mirco microplate reader of Multiskan at 450 nm and compared with the standard curve. Serum Scr level was detected by a Roche P800 automatic biochemical analyzer and matching reagents (Roche Instrument Center, Switzerland). Serum uric acid was tested through enzyme methods, and the kits were all purchased from Beckman-Coulter.

Outcome measures

The serum vitamin A and E levels of pregnant women in both groups were compared, and the correlation between the two levels and diseases of pregnant women was analyzed. The levels of renal injury markers were compared, and the correlation between vitamins A, E and various markers of kidney injury was analyzed.

Statistical analysis

The relevant data were analyzed via SPSS 19.0 (Asia Analytics Formerly SPSS China). The counting data were expressed by rate and analyzed by χ^2 test. The measurement data were expressed by mean ± sd. The inter-group comparison was analyzed by Spearman, while the intra-group comparison was assessed by Pearson. The diagnostic value was assessed by ROC curve. P < 0.05 has statistical significance.

Results

General data

There was no difference in age, BMI, history of smoking and family history between the two groups (P > 0.05), but the blood pressure, urine protein, AST, ALT, β2-microglobulin and eGFR of patients in the SPE and AKI group were higher than those in the SPE group; and the gestational weeks at delivery were lower than that in the SPE group, with statistical significance (P < 0.05) (**Table 1**).

Predictive value of vitamins A and E in PE and AKI

According to the results of statistical analysis, the vitamin levels of patients in the SPE and AKI group were lower than those in the SPE group, and the difference was statistically remarkable (P < 0.001). Further ROC analysis revealed that the predictive value of vitamin A for PE with AUC, had a 95% confidence interval, sensitivity, specificity and diagnostic levels which were 0.8608, 0.8104 to 0.9112, 79.25%, 74.44%, and 0.345, respectively. Those of vitamin E for PE were 0.8574, 0.8053 to 0.9095, 80.19%, 75.56% and 10.06, respectively. Furthermore, we also found that the levels were negatively correlated with PE severity, and those in patients with SPE and AKI decreased further (P < 0.001); their correlation coefficients were r=-0.570, P < 0.001, r=-0.709, P < 0.001, respectively (**Figure 1**).

Adverse outcomes of PE and postpartum kidney injury patients

In 106 SPE patients and those with SPE and AKI, 86 cases had abnormal vitamin A and E

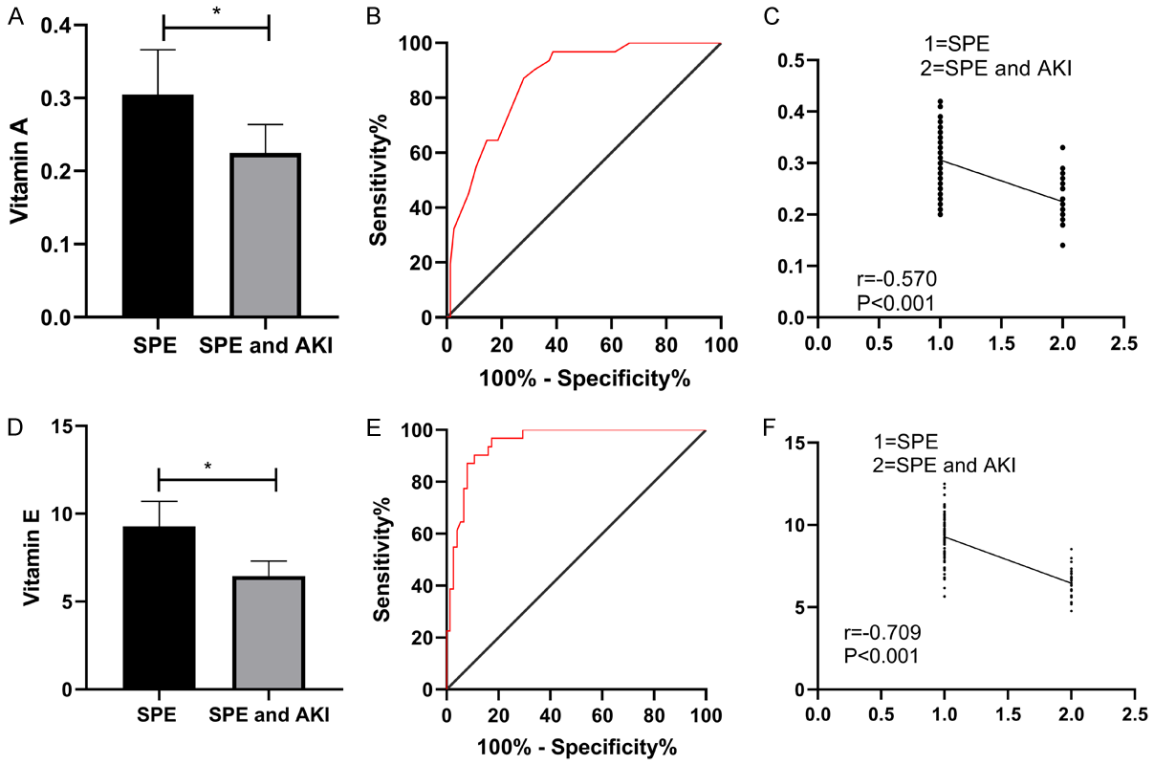

Figure 1. Diagnostic analysis of vitamins A and E levels in PE. A: Expression of vitamin A in different groups; B: Diagnostic value of vitamin A in PE; C: Correlation between vitamin A and PE severity; D: Expression of vitamin E in different groups; E: Diagnostic value of vitamin E in PE; F: Correlation between vitamin E and PE severity. * denotes $P < 0.05$.

levels and 20 had normal levels. According to whether vitamin levels were abnormal or not, adverse outcomes were divided as follows: low levels of vitamin A included 11 cases with severe postpartum hemorrhage, 9 with placental abruption, 3 with HELLP syndrome and 6 with basic kidney diseases. Other causes included 2 cases with eclampsia, 4 with cerebrovascular accident (CVA), 2 with liver disease, 7 with neonatal asphyxia, 13 with fetal distress, 10 with FGR and 3 with stillbirth. Normal vitamin A levels included 2 cases of placental abruption, 5 of basic kidney disease, 3 of neonatal asphyxia, 2 of fetal distress, 5 of FGR and 1 stillbirth. Abnormal vitamin E levels included severe postpartum hemorrhage in 10 cases, placental abruption in 9, HELLP syndrome in 7, and basic kidney disease in 4 patients. Other causes included eclampsia in 2 cases, CVA in 1, liver disease in 1, neonatal asphyxia in 9, fetal distress in 9, FGR in 13 and stillbirth in 3. Normal vitamin E levels included 3 cases with placental abruption, 4 with basic kidney disease, 2 with neonatal asphyxia, 1 with fetal distress, 6 with FGR and 1 with stillbirth. The differences of vitamin A and E levels in patients with basic kidney diseases were statistically marked ($P < 0.05$). Besides, vitamins A and E had no statistical significance in adverse outcomes ($P > 0.05$) (**Table 2**).

Expression of renal injury markers in patients with PE and postpartum renal injury

The levels of renal injury markers KIM-1, NGAL, Scr and UA in SPE patients and patients SPE complicated with AKI were detected. The results revealed that urine KIM-1, NGAL, Scr and UA in SPE and AKI group were obviously higher than those in the SPE group, and the differences were statistically marked ($P < 0.05$) (**Table 3**).

Correlation between renal injury markers and survival level in PE and postpartum kidney injury

Pearson analysis showed that vitamin A and E levels were negatively correlated with all kinds

Table 2. Classification of adverse outcomes in patients with PE and postpartum kidney injury (n; %)

Category	Abnormal low vitamin A (n=86)	Normal vitamin A (n=20)	χ^2/t	P	Abnormal low vitamin E (n=86)	Normal vitamin E (n=20)	χ^2/t	P
Severe postpartum hemorrhage	11 (12.79)	0 (0.00)	-	0.120	10 (11.63)	0 (0.00)	-	0.203
Placental abruption	9 (10.47)	2 (10.0)	0.004	0.951	9 (10.47)	3 (15.0)	0.332	0.564
HELLP syndrome	3 (3.49)	0 (0.00)	-	> 0.999	7 (8.14)	0 (0.00)	-	0.343
Basic kidney disease	6 (6.98)	5 (25.00)	5.667	0.017	4 (4.65)	4 (20.00)	5.479	0.019
Eclampsia	2 (2.33)	0 (0.00)	-	> 0.999	2 (2.33)	0 (0.00)	-	> 0.999
Cerebrovascular accident	4 (4.65)	0 (0.00)	-	> 0.999	1 (1.16)	0 (0.00)	-	> 0.999
Liver diseases	2 (2.33)	0 (0.00)	-	> 0.999	1 (1.16)	0 (0.00)	-	> 0.999
Neonatal asphyxia	7 (8.14)	3 (15.00)	0.894	0.344	9 (10.47)	2 (10.00)	0.003	0.951
Fetal distress	13 (15.12)	2 (10.00)	0.350	0.554	9 (10.47)	1 (5.00)	0.567	0.451
Fetal growth restriction	10 (11.63)	5 (25.00)	2.388	0.122	13 (15.12)	6 (30.00)	2.443	0.118
Stillbirth	3 (3.49)	1 (5.00)	0.102	0.749	3 (3.49)	1 (5.00)	0.102	0.749

Note: A patient can have two or more diseases.

Table 3. Expression of renal injury markers

Group	KIM-1 (ng/mL)	NGAL (ng/mL)	UA (umol·L)	Scr (umol·L^{-1})
SPE (n=75)	7.18±1.39	14.36±2.20	366.26±31.99	112.18±21.99
SPE and AKI (n=31)	8.36±1.53	16.51±2.54	395.63±51.74	123.70±31.63
t	3.860	4.372	3.551	2.145
P	< 0.001	< 0.001	< 0.001	0.034

of renal injury markers (P < 0.001), and when the levels decreased, all markers increased. The correlation coefficients of vitamin A with KIM-1, NGAL, UA and Scr were r=-0.754, r=-0.816, r=-0.845 and r=-0.760, respectively. Those of vitamin E with KIM-1, NGAL, UA and Scr were r=-0.760, r=-0.825, r=-0.855, r=-0.777, respectively (All P < 0.001, **Figure 2**).

Discussion

PE is one of the main causes of maternal mortality in the world, and it can lead to poor health of both mothers and babies, and may also bring about other serious maternal and infant complications, including stroke, eclampsia and organ failure. Adverse perinatal outcomes of fetuses and newborns include intrauterine growth restriction, low birth weight and stillbirth [22]. One of the most common causes of AKI is eclampsia. AKI in pregnant women with PE or eclampsia will not only lead to maternal mortality and morbidity, but also result in poor fetal prognosis [23, 24]. The increase of free radicals and oxidative stress caused by insufficient antioxidant defense ability are one of the causes of PE, but there is no effective strategy to prevent PE at present [25]. Therefore, early prediction and effective prevention are of great significance to PE prevention and cure.

Recently, vitamin levels have been reported to be involved in PE progression. For example, the risk factors of PE include vitamin A deficiency [26], and the probability of severe PE in pregnant women with vitamin D deficiency has increased by more than three times [27]. In addition, the high level of lipid peroxidation and the decrease of vitamin E and C levels (related to antioxidant activity) may be related to PE pathophysiology and pathogenesis [28]. These studies show that low vitamin levels are relevant to PE onset. Our research reported that the vitamin levels in severe PE patients gradually decreased with disease severity, which was consistent with these findings and negatively correlated with disease severity. The vitamin A and E levels further decreased in kidney injury patients, and the sensitivity and specificity of the latter were slightly higher than those of the former.

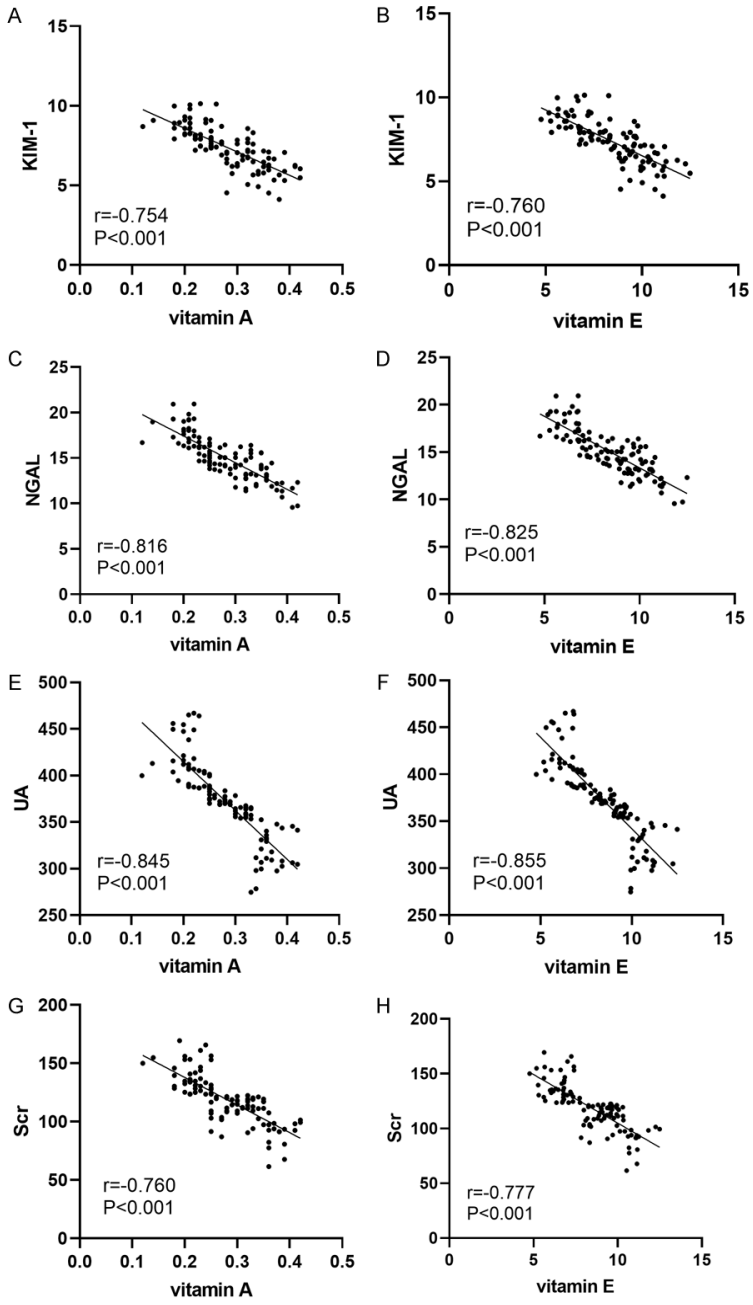

Figure 2. Correlation between different renal injury markers and vitamin A and E levels. A: Relationship between vitamin A and KIM-1; B: Relationship between vitamin E and KIM-1; C: Relationship between vitamin A and NGAL; D: Relationship between vitamin E and NGAL; E: Relationship between vitamin A and UA; F: Relationship between vitamin E and UA; G: Relationship between vitamin A and Scr; H: Relationship between vitamin E and Scr.

Other studies have shown that markers of proximal tubular injury, such as KIM-1, NGAL and retinol binding protein (RBP), in the urine of PE patients are higher than those of healthy pregnant women [29]. Moreover, we also found that vitamin level was tied to kidney injury markers. Some studies have shown that vitamin E can protect the kidney from cisplatin-induced nephrotoxicity, because it can reduce KIM-1, a kidney injury molecule [30]. AKI with high blood urea, high creatinine and kidney tissue damage caused by monosodium glutamate can be inhibited by vitamin E [31]. These studies have shown that high levels of vitamins can reduce the level of renal injury markers, while we found that low levels of vitamin A and E were negatively correlated with renal injury markers (KIM-1, NGAL, UA, Scr), and the level of renal injury markers was further increased in patients with PE and postpartum kidney injury. Thus, these findings indicate that a low expression level of vitamins A and E is negatively correlated with PE and postpartum kidney injury, while the latter has higher sensitivity and specificity than the former.

To sum up, the levels of vitamin A and E are low in patients with PE and postpartum kidney injury and are negatively correlated with markers of kidney injury, which may be used as physical and chemical indicators for clinical prediction. However, there are still some shortcomings in our study. For example, a single-center study with small patient numbers isn't enough; therefore a further multi-center and larger sample clinical research study needs to be conducted to clarify the predictive significance of vitamins A and E.

Disclosure of conflict of interest

None.

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