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Exploration of the Relationship Between Aldehyde Dehydrogenase 2 Gene Polymorphisms and Venous Thromboembolism in Critically Ill Patients

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Abstract: *Objective*: Whether patients with venous thromboembolism (VTE) receive targeted treatment or not, their mortality rates remain relatively high. Common risk factors for VTE include tumors, trauma, obesity, infection, and gene mutations related to the coagulation/anticoagulation system. However, research on the relationship between non-coagulation/anticoagulation system gene mutations and VTE is currently insufficient. *Methods*: This study retrospectively collected clinical data from 123 patients in the Department of Critical Care Medicine at Nanjing Jiangning Hospital from June 1, 2023, to December 31, 2024. Through univariate and multivariate analyses, risk factors for VTE in critically ill patients were identified, and a risk prediction model was constructed. *Results*: The proportion of patients carrying the ALDH2*2 genotype was higher in the VTE group than in those with the ALDH2*1 genotype (21.3% vs 7.9%, $P = 0.032$). Patients carrying the ALDH2*2 genotype had a 6.553-fold increased risk of developing VTE compared to those with the ALDH2*1 genotype. Patients with a history of diabetes had an 11.491-fold increased risk of VTE compared to those without diabetes, while patients with a history of smoking had a 39.302-fold increased risk compared to non-smokers. For each additional year of age, the risk of VTE increased by 12.5%. For each one-unit increase in left ventricular shortening fraction, the risk of VTE decreased by 37.4%. *Conclusion*: Mutation of the mitochondrial metabolic enzyme ALDH2 is a risk factor for VTE in critically ill patients and may represent a novel pathway for VTE prevention in this population.

Keywords: Acetaldehyde dehydrogenase 2; Intensive medicine; Venous thromboembolism; Risk prediction

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1. Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary thromboembolism, carries

an approximate mortality rate of 25% in untreated cases, while the short-term mortality rate among treated VTE patients ranges from 15 to 30%. Risk factors for VTE include malignancy, antiphospholipid antibody syndrome, prolonged immobilization, trauma, obesity, estrogen therapy, infection, and others [1]. Several studies have identified anticoagulant-related factors (protein S, protein C, antithrombin) and procoagulant-related factors (coagulation factors I/II/V/VIII/IX/XI, vWF) as hereditary risk factors for VTE [2–5]. Lindström reported 16 genetic loci predisposing to VTE in European and African American populations [6]. Research focusing on the Chinese population has revealed that mutations in gene loci related to the protein C anticoagulant system increase the risk of VTE by 2.5 to 6.4 times [7,8]. However, research on non-coagulation/anticoagulation system genes and VTE remains insufficient.

Acetaldehyde dehydrogenase (ALDH) is one of the key enzymes involved in ethanol metabolism, encompassing ALDH1 and ALDH2. The enzyme encoded by ALDH2*1/*1 exhibits normal activity and is generally denoted as ALDH2*1, whereas the mutant form of ALDH2 is labeled as ALDH2*2, which includes genotypes ALDH2*1/*2 and ALDH2*2/*2. The enzyme encoded by ALDH2*1/*2 retains only 30–40% of the normal enzymatic activity, while the enzyme encoded by ALDH2*2/*2 exhibits almost no activity [9]. The mutation frequency of ALDH2 in the Asian population ranges from 30–50%, significantly higher than that in Western populations. ALDH2 can prevent the accumulation of reactive oxygen species that damage tissues and organs, and mice with the ALDH2 gene knocked out exhibit pronounced vascular endothelial injury and vascular dysfunction [10]. ALDH2 activation can alleviate lung injury by inhibiting oxidative stress and reversing alveolar epithelial cell dysfunction [11]. Critically ill patients often present with vascular endothelial injury and an inflammatory state, which triggers the coagulation cascade and promotes thrombus formation. The thrombus, in turn, activates immune cells and exacerbates inflammation [12]. ALDH2 may serve as an effective intervention target for the vicious cycle of "coagulation-inflammation".

This study preliminarily explores the association between ALDH2 gene polymorphisms, which are not part of the coagulation/anticoagulation system, and VTE in critically ill patients. The aim is to enhance healthcare professionals' understanding of VTE, facilitate effective screening of VTE patients, and improve the standardized prevention rate of VTE.

2. Methodology

2.1. Study design and participants

This study is a cross-sectional study that retrospectively collected clinical data from patients in the Intensive Care Unit of Jiangning Hospital Affiliated to Nanjing Medical University from June 1, 2023, to December 31, 2024. Ultimately, 123 critically ill patients were included.

The inclusion criteria are as follows:

(1) Age ≥ 18 years old;

(2) No prior history of VTE.

The exclusion criteria are as follows:

(1) Patients with tumors, antiphospholipid antibody syndrome, major trauma or fractures, surgical patients, or pregnant women;

(2) Patients who refuse ALDH2 genotyping;

(3) Patients who refuse to sign the informed consent form.

2.2. Clinical diagnosis of VTE

All enrolled patients underwent duplex ultrasound examination of both lower extremities on the second day of admission to check for deep vein thrombosis (DVT) or spiral CT pulmonary angiography during hospitalization to detect pulmonary embolism (PE). The collected ultrasound or spiral CT pulmonary angiography images underwent quality control by the Ultrasound Department and Imaging Department of Jiangning Hospital Affiliated to Nanjing Medical University.

2.3. Laboratory examination

DNA was extracted and amplified from the patients' venous blood using a DNA extraction kit (Takara Bio). Subsequently, the ALDH2 genotype was determined using an ALDH2 gene polymorphism detection kit (Hybribio).

2.4. Statistical analysis

This study employed SPSS software (IBM SPSS Statistics, IBM Corp.) for statistical analysis. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables conforming to a normal distribution were expressed as mean ± standard deviation (SD), and inter-group comparisons were conducted using the t-test. Variables with a non-normal distribution were represented by median (interquartile range), and inter-group comparisons were performed using the Wilcoxon rank-sum test. Categorical variables were presented as frequencies and percentages, and differences between groups were compared using the χ^2 test or Fisher's exact test. A P-value < 0.05 was considered statistically significant.

Variables that showed statistical significance in the univariate analysis were included in the multivariate analysis. A forward stepwise regression strategy was adopted to screen for variables that still exhibited statistical significance. Using these variables as independent variables and the occurrence of VTE as the dependent variable, a binary logistic regression was employed to establish a risk prediction model.

3. Results

3.1. Analysis of clinical characteristics of patients with Non-VTE and VTE

In this study, clinical data from 123 critically ill patients were collected. Statistically significant differences in ALDH2 genotypes were observed between the VTE group and the non-VTE group, with the ALDH2*2 genotype being more prevalent in the VTE group than the ALDH2*1 genotype (**Table 1**, 21.3% vs 7.9%). Diabetes and a history of cerebral infarction also showed statistically significant differences between the two groups. The proportion of patients with a history of diabetes was higher in the VTE group (**Table 1**, 17.7% vs 4.5%), as was the proportion of patients with a history of cerebral infarction (**Table 1**, 28.6% vs 8.4%). The proportion of patients with a history of alcohol consumption was lower in the VTE group (17.2% vs 0%), which may be related to the weak alcohol metabolism capacity and restricted alcohol consumption in patients with the ALDH2*2 genotype. The creatinine level in the VTE group was higher than that in the non-VTE group, while the fractional shortening was lower in the VTE group compared to the non-VTE group, with both differences being statistically significant (**Table 1**).

Table 1. Clinical characteristics of patients with non-VTE and VTE

Variable	Category	Non-VTE[a] (n=107)	VTE[a] (n = 16)	*P*-value	Correlation coefficient (r)
ALDH2	ALDH2*1	70 (92.1)	6 (7.9)	0.032	0.190
	ALDH2*2	37 (78.7)	10 (21.3)		
Gender	Male	72 (88.9)	9 (11.1)	0.385	0.078
	Female	35 (83.3)	7 (16.7)		
Coronary heart disease	No	31 (88.6)	4 (11.4)	0.975	0.03
	Yes	76 (86.4)	12 (13.6)		
Diabetes	No	42 (95.5)	2 (4.5)	0.037	0.185
	Yes	65 (82.3)	14 (17.7)		
Hypertension	No	25 (92.6)	2 (7.4)	0.512	0.088
	Yes	82 (85.4)	14 (14.6)		
Atrial fibrillation	No	90 (88.2)	12 (11.8)	0.584	0.081
	Yes	17 (81.0)	4 (19.0)		
Cerebral infarction	No	87 (91.6)	8 (8.4)	0.014	0.244
	Yes	20 (71.4)	8 (28.6)		
Smoking history	No	42 (97.7)	1 (2.3)	0.010	0.227
	Yes	65 (81.3)	15 (18.8)		
Drinking history	No	77 (82.8)	16 (17.2)	0.034	0.215
	Yes	30 (100.0)	0 (0.0)		
Age		66.3 ± 11.7	75.7 ± 9.2	0.003	0.267
BMI		24.97 (23.44, 27.01)	24.50 (21.57, 25.36)	0.180	-0.122
White blood		6.68 (5.15, 8.03)	5.70 (4.09, 6.41)	0.009	-0.236
Hemoglobin		133.55 ± 16.82	122.69 ± 22.19	0.023	-0.205
Sodium		141.0 (139.4, 143.0)	142.1 (139.7, 143.1)	0.357	0.083
Chloride		103.5 (101.3, 105.3)	104.9 (101.8, 105.9)	0.196	0.117
Creatinine		74 (65, 88)	83 (74, 112)	0.026	0.202
ALT		23 (15, 33)	16 (13, 21)	0.076	-0.160
AST		21 (17, 27)	20 (17, 26)	0.447	-0.069
PASP		39 (38, 44)	41 (39, 43)	0.494	0.062
EF		65 (62, 66)	63 (61, 65)	0.075	-0.161
FS		35 (34, 36)	34 (33, 35)	0.049	-0.178

a: Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables are presented as frequency (percentage); ALDH2: Aldehyde dehydrogenase 2; VTE: Venous thromboembolism; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PASP: Pulmonary artery pressure; EF: Left ventricular ejection fraction; FS: Left ventricular fractional shortening

3.2. Multifactorial logistic regression analysis of the risk of VTE occurrence

Variables with a *P*-value less than 0.05 in the univariate analysis, including age, ALDH2 genotype, history of diabetes, history of cerebral infarction, history of smoking, history of alcohol consumption, total white blood cell count, hemoglobin content, creatinine, and fractional shortening, were included in the multifactorial logistic regression analysis. The multifactorial analysis revealed statistically significant differences in age, ALDH2 genotype, history of diabetes, history of smoking, and fractional shortening (**Table 2**).

For each additional year of age, the risk of VTE occurrence increased by 12.5% (**Table 2**, OR = 1.125, 95% CI: 1.034–1.223, *P* = 0.006); patients with the ALDH2*2 genotype had a 6.553-fold higher risk of VTE compared to those with the ALDH2*1 genotype (**Table 2**, 95% CI: 1.521–28.226, *P* = 0.012); patients with a history of diabetes had an 11.491-fold higher risk of VTE compared to those without a history of diabetes (**Table 2**, 95% CI: 1.667–93.620, *P* = 0.014); patients with a history of smoking had a 39.302-fold higher risk of VTE compared to those without a history of smoking (**Table 2**, OR = 39.302, 95% CI: 1.930–800.402, *P* = 0.017); for each unit increase in fractional shortening, the risk of VTE occurrence decreased by 37.4% (**Table 2**, OR = 0.626, 95% CI: 0.457–0.859, *P* = 0.004).

Table 2. Results of multifactorial regression analysis

Variable	B	S.E.	Wald	P	Exp (B) [OR]	95% CI	
ALDH2	1.880	0.745	6.366	0.012	6.553	1.521	28.226
Diabetes	2.525	1.028	6.037	0.014	12.491	1.667	93.620
Smoking	3.671	1.538	5.700	0.017	39.302	1.930	800.402
Age	0.118	0.043	7.574	0.006	1.125	1.034	1.223
FS	-0.468	0.161	8.415	0.004	0.626	0.457	0.859
Constant	-0.472	4.162	0.013	0.910	0.624	-	

ALDH2: Aldehyde Dehydrogenase 2; FS: Left Ventricular Fractional Shortening

3.3. ROC curve analysis of VTE risk prediction model

A VTE risk prediction model for critically ill patients was constructed using variables selected through multivariate analysis, and the theoretical probability of VTE occurrence in enrolled patients was calculated. The ROC curve was plotted using MedCalc software. The five-variable model, which included age, ALDH2 genotype, history of diabetes, history of smoking, and fractional shortening, had an area under the curve (AUC) of 0.901, indicating good discriminatory power of the model. Each of the aforementioned variables was removed separately to reconstruct four-variable models. After DeLong testing, it was found that removing the fractional shortening or diabetes variables resulted in a decrease in the model's AUC to 0.802 and 0.851, respectively, with statistically significant differences. This suggests that fractional shortening and history of diabetes make relatively important contributions to the model's predictive ability (**Table 3**, **Figure 1**). The model's AUC decreased from 0.901 to 0.872 after removing the ALDH2 genotype, but this difference did not reach statistical significance.

Table 3. Comparison of VTE risk assessment models in critically Ill patients

Model	AUC	S.E.	95% CI	Z	P
Five-Variable Model	0.901	0.0347	0.834–0.947		
Four-Variable Model (excluding ALDH2)	0.872	0.0404	0.800–0.925	1.121	0.262
Four-Variable Model (excluding Diabetes)	0.851	0.0429	0.775–0.909	2.132	0.033
Four-Variable Model (excluding FS)	0.802	0.0505	0.721–0.868	2.579	0.010
Four-Variable Model (excluding Age)	0.860	0.0488	0.786–0.916	1.103	0.270
Four-Variable Model (excluding Smoking)	0.833	0.0525	0.755–0.894	1.508	0.132

ALDH2: Aldehyde dehydrogenase 2; FS: Left ventricular fractional shortening

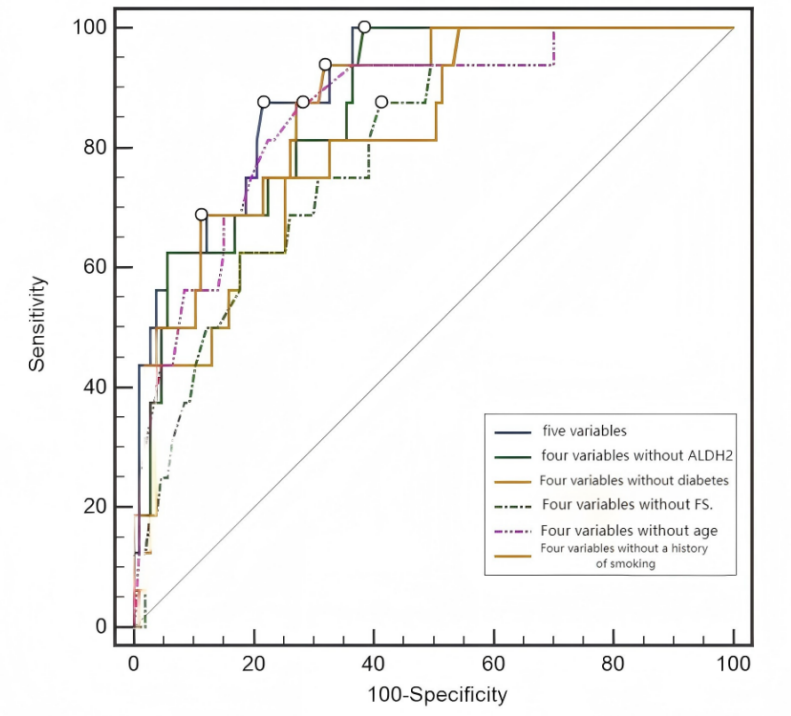

Figure 1. ROC curve of VTE risk assessment model in critically Ill patients.

4. Discussion

ALDH2, a metabolic enzyme localized in mitochondria, plays a crucial role in clearing toxic lipid peroxides. Critically ill patients often experience stress and inflammatory activation, leading to an increase in reactive oxygen species (ROS). This, in turn, triggers lipid peroxidation in organelles, resulting in vascular endothelial cell dysfunction and promoting thrombosis. Our research has found that patients with ALDH2 gene mutations are more prone to developing VTE. Previous studies have revealed that ALDH2 activity in coronary atherosclerotic tissues is lower than that in normal tissues [13]. The application of the ALDH2 agonist Alda-1 can reverse LPS-induced cardiac dysfunction, suggesting that targeted intervention of ALDH2 may prevent the occurrence and progression of VTE [14].

Hyperglycemia can trigger multiple signaling pathways that damage vascular endothelium, and diabetic patients often exhibit a hypercoagulable state, increasing the risk of VTE. Research by Heit *et al.* indicates that

fasting blood glucose levels ≥ 140 mg/dL or the presence of diabetes complications are associated with VTE, highlighting the importance of blood glucose regulation in critically ill patients to reduce the risk of VTE [15]. A meta-analysis has shown that smoking is associated with an increased risk of VTE, with a risk ratio of 1.38 [16]. Harmful substances such as nicotine can promote platelet aggregation and increase blood viscosity, leading to thrombosis. Previous studies have demonstrated that the incidence of VTE remains constant among males across all age groups, but the incidence of VTE in females over 60 years old increases compared to females under 55 years old [17]. Our study is limited by the sample size and lacks subgroup analysis stratified by age. However, the results indicate that patients in the VTE group are significantly older than those in the non-VTE group, suggesting that endothelial dysfunction caused by aging is a crucial factor in VTE formation [18]. Pastori's research has demonstrated that heart failure, atrial fibrillation, and myocardial infarction events within three months prior to admission are strong risk factors for VTE [19]. This study reveals a significant decrease in the left ventricular fractional shortening in patients in the VTE group. This association can be explained by cardiac pump failure and slow venous return in patients.

This study preliminarily reveals the relationship between ALDH2 gene polymorphism and VTE in critically ill patients and constructs a VTE risk assessment model for such patients. Incorporating ALDH2 gene polymorphism, an indicator with regional distribution differences, will further enrich the domestic VTE risk assessment system and provide data and theoretical support for the early detection and intervention of VTE. Due to the relatively small sample size of the study, some potential influencing factors may not have been effectively identified. Subsequent research should involve multi-center collaboration to further expand the sample size, optimize the predictive model, conduct external data validation, and enhance the stability and generalizability of the model.

5. Conclusion

The mutation of the mitochondrial metabolic enzyme ALDH2 constitutes a risk factor for the development of VTE in critically ill patients. This finding highlights a potential novel pathway for VTE prevention in this vulnerable population.

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Disclosure statement

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