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Original Article

Internal relationship between symptomatic venous thromboembolism and risk factors: up-regulation of integrin β1, β2 and β3 levels

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Abstract: Background: To compare different expression of core proteins among venous thromboembolism (VTE) and those with risk factor groups and analyze the relative risk for VTE after integrating integrin β1, β2 and β3 expression. Methods: A total of 1006 subjects were recruited and divided into VTE group, risk factor groups and control (non- risk factor) group. Flow cytometry was performed to detect the expression of integrin β1, β2 and β3. The relative risk for VTE was evaluated with independent, parallel and serial methods. Results: The expression of integrin β1 increased markedly in VTE patients, and those with risk factors (acute infection, malignancy, and autoimmune diseases), respectively ($P < 0.001$ or 0.01). The expression of integrin β1 in trauma/surgery group was not significantly different with control group ($P > 0.05$). The expression of integrin β2 or β3 significantly increased in VTE group, but that in risk factor groups was not significantly increased ($P > 0.05$). Multivariate analysis revealed the trauma/surgery groups had no significantly increased risk for VTE. Conclusions: VTE group patients have significantly increased expression of integrin β1, β2 and β3, and risk factor groups (acute infection, malignancy and autoimmune disease) have significantly increased expression of integrin β1. The significant increase in integrin β2, β3 expression is a marker differentiating of VTE group patients with other risk factor groups. Trauma/surgery group has no increased expression of integrin β1, β2 and β3 as other risk factors. Thus, that trauma/surgery may be not the "true" risk factor for VTE.

Keywords: Venous thromboembolism, risk factor, integrin β1, β2 and β3

Introduction

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary thromboembolism (PE). PE has been a major health problem world wide due to its high morbidity, high mortality and high misdiagnosis rate [1]. Clinically apparent VTE can be divided into hereditary or acquired, with a majority of VTE being acquired.

American College of Chest Physicians has published the Guideline for the Diagnosis, Therapy and Prevention of VTE since 1995 and the 9th edition was published in 2012 [2, 3]. This guideline proposes that infection, malignancy, autoimmune diseases, trauma, surgery, family history and advanced age are risk factors for VTE. Risk factors are determined on the basis of evidence based medicine, and subjects with these risk factors are susceptible to VTE, but the specific mechanism is still unclear. In clinical practice, there are no specific objective protein indicators of VTE, and it is not possible to objectively evaluate the risks for VTE.

Acute venous thrombosis is mainly red thrombus which is susceptible to being broken down

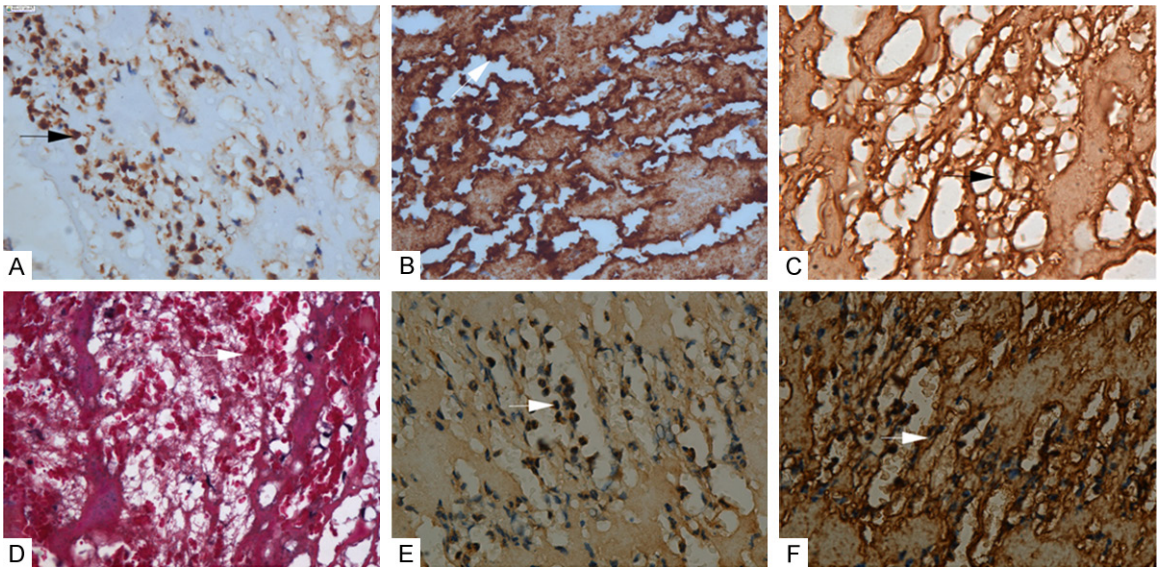

Figure 1. A. Arrow: dark-stained integrin β2 was expressed on the neutrophils (× 400). B. Arrow: dark-brown integrin β3 was expressed on platelets and on the coral-like skeleton formed by platelets. (× 200). C. Arrow: (Platelets and neutrophils bound fibrinogen to construct mesh-like structure(× 400). D. Arrow: Mesh-like structure was nest-like biological filter (× 400, Masson staining), in which red blood cell dominant blood cells filled. E. Arrow: dark-brown factor X was found on the surface of the neutrophils (× 400). F. Arrow: dark-brown factor Xa was found on the surface of mesh-like structure (× 400). This suggests factor Xa acts on the fibrinogen/fibrin.

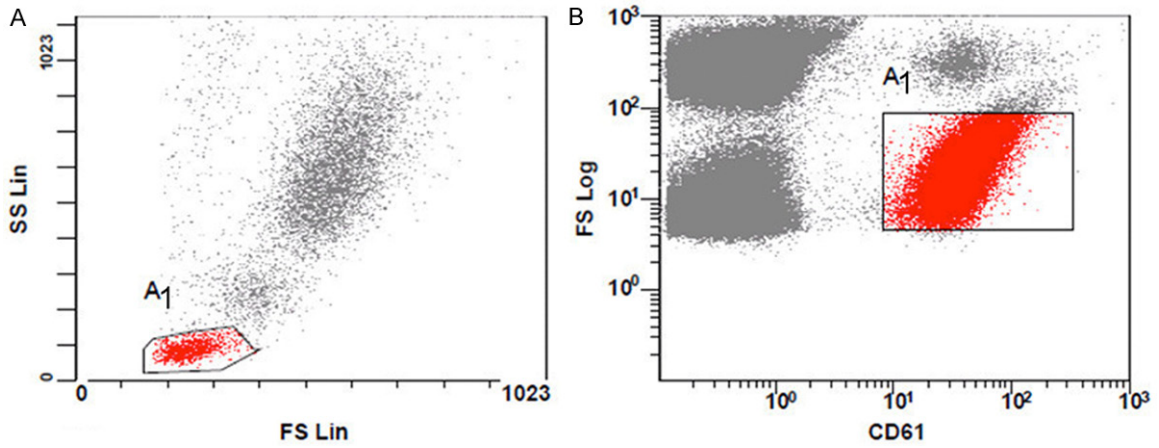

Figure 2. A. Detection of lymphocytes with CD18 and CD29 gating, A1, represents the scatter diagram. Relevant cell population was selected while gating, and cell fragment and other cells are excluded. B. Detection of platelets with CD61 gating, A1, represents the scatter diagram. Relevant cell population was selected while gating, and cell fragment and other cells are excluded.

and autolyzing. In acute venous thrombosis, where delayed thrombolysis and catheter thrombectomy are often effective, we reported that the red thrombus is mainly composed of fibrinogens, possibly explaining the reason for thrombus autolysis and the therapeutic efficacy of delayed thrombolysis and catheterization in VTE [4]. In our study, tandem mass spectrometry was performed to analyze the red thrombus in acute PE, and showed the core protein of this red thrombus were mainly integrins β1, β2 and β3. Furthermore, immunohistochemistry confirmed that the dark brown integrin β1, β2 and β3 were mainly localized on the lymphocytes, white blood cells and platelets within the thrombus. The integrin β2 and β3 on the white blood cells and platelets can bind to ligand fibrinogens forming filament-like networks, whi-

Table 1. Baseline data of 1006 subjects

Variables	Group	VTE	INF	CAN	IMD	SUR	CONTROL	TOTAL
		N = 72	N = 330	N = 144	N = 103	N = 111	N = 246	N = 1006
Age	Mean ± SD	64.86 ± 15.58	76.15 ± 12.80	67.36 ± 12.67	56.86 ± 14.22	51.07 ± 18.72	68.35 ± 13.62	67.40 ± 16.26
Gender	Male (%)	32 (44.44)	196 (59.39)	90 (62.50)	19 (18.63)	69 (62.16)	128 (52.03)	534 (53.08)
	Female (%)	44 (55.56)	134 (40.61)	54 (37.50)	83 (81.37)	42 (37.84)	118 (47.97)	472 (46.92)
β1	Mean ± SD	13.42 ± 5.22	11.37 ± 6.39	12.34 ± 5.40	11.48 ± 5.45	10.24 ± 6.33	9.74 ± 4.62	11.15 ± 5.76
	Low (n, %)	1 (1.39)	18 (5.45)	0 (0.00)	2 (1.96)	5 (4.50)	7 (2.85)	33 (3.28)
	Normal (n, %)	40 (55.56)	214 (64.85)	95 (65.97)	68 (66.67)	85 (76.58)	206 (83.74)	708 (70.45)
	High (n, %)	31 (43.06)	98 (29.70)	49 (34.03)	32 (31.37)	21 (18.92)	3 (13.41)	264 (26.27)
β2*	Median	94.70 (76.30, 98.71)	91.9 (87.50, 98.80)	91.40 (76.90, 98.50)	91.10 (75.20, 98.60)	91.00 (71.90, 98.40)	90.50 (75.60, 97.90)	91.40 (75.20, 98.60)
	Low (n, %)	1 (1.45)	20 (6.27)	2 (1.40)	3 (3.19)	6 (5.41)	9 (3.67)	41 (4.18)
	Normal (n, %)	39 (56.52)	197 (61.76)	109 (76.22)	62 (65.96)	89 (80.18)	202 (82.45)	698 (71.15)
	High (n, %)	29 (42.03)	102 (31.97)	32 (22.38)	29 (30.85)	16 (14.41)	34 (13.88)	242 (24.67)
β3	Mean ± SD	11.05 ± 4.05	9.79 ± 4.07	10.33 ± 3.55	10.21 ± 4.03	8.74 ± 2.43	9.27 ± 3.02	9.76 ± 3.64
	Low (n, %)	1 (1.39)	21 (6.36)	2 (1.39)	4 (3.92)	3 (2.70)	12 (4.88)	43 (4.28)
	Normal (n, %)	57 (79.17)	272 (82.42)	124 (86.11)	87 (85.29)	107 (96.40)	226 (91.87)	873 (86.87)
	High (n, %)	14 (19.44)	37 (11.21)	18 (12.50)	11 (10.78)	1 (0.90)	8 (3.25)	89 (8.86)

Footnotes: *indicates non normal distribution. [Control value range] β1: 3.14-13.90; β2: 73.40-95.30; β3: 4.39-14.71.

Table 2. Single-factor analysis of integrin β1, β2, β3 level

	VTE			INF			CAN			IMD			SUR		
	x^2	OR*	95% CI	x^2	OR*	95% CI	x^2	OR*	95% CI	x^2	OR*	95% CI	x^2	OR*	95% CI
β1	30.44	4.88	2.69, 8.83	21.94	2.76	1.78, 4.27	23.24	3.33	2.01, 5.50	14.92	2.91	1.67, 5.07	1.80	1.50	0.82, 2.74
β2	22.52	3.93	2.18, 7.09	21.15	2.64	1.73, 4.04	4.97	1.80	1.07, 3.04	8.75	2.28	1.31, 3.98	0.03	0.98	0.52, 1.85
β3	22.67	7.18	2.87, 17.9	12.39	3.75	1.71, 8.22	12.48	4.25	1.79, 10.04	7.78	3.55	1.38, 9.12	1.72	0.27	0.03, 2.19

Footnote: *indicates VTE, INF, CAN, IMD, SUR vs. CONTROL. The integrin level higher than the control upper limit is defined as positive, and lower than the upper limit is defined as the negative. The relationships between integrin β1, β2, β3 positive exposure and the occurrence of VTE, between VTE group, risk factor groups and control group were compared. The OR value in β1 positive population was 4.88 (95% CI: 2.69-8.83) higher than β1 negative population. In risk factor groups, the highest OR value of 3.33 (95% CI: 2.01-5.50) was found in the malignancy group. The OR value in β2 positive population was 3.93 (95% CI: 2.18-7.09) higher than β2 negative population. In risk factor groups, the highest OR value of 2.64 (95% CI: 1.73-4.04) was found in the acute infection group. The OR value of integrin β3 positive population was 7.18 (95% CI: 2.87-17.92) in VTE group.

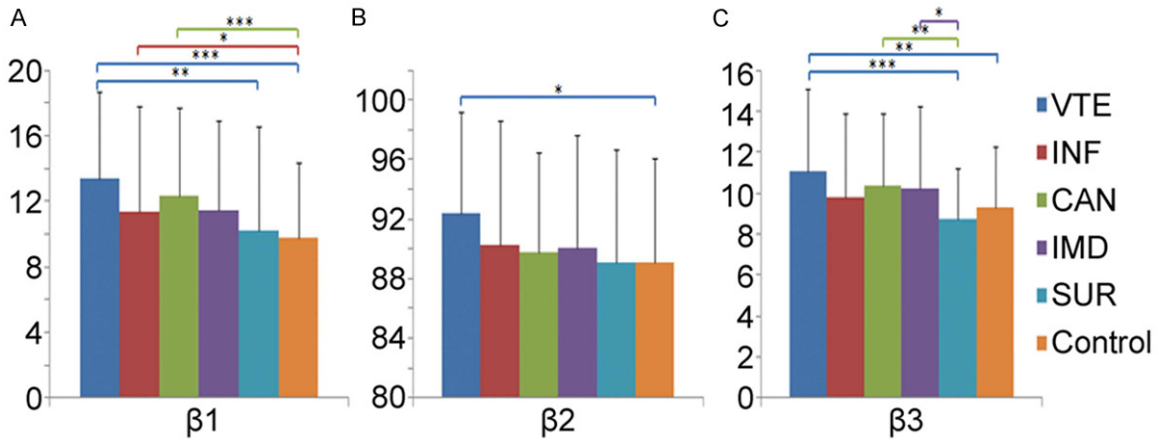

Figure 3. Differences of β1, β2, and β3 among groups. A. There is significant difference between VTE (INF and CAN) and control group for β1, VTE and SUR group for β1. B. There is significant difference between VTE and control group for β2. C. There is significant difference between VTE and control group for β3, VTE and SUR group for β3. *indicates $p < 0.05$; **indicates $p < 0.01$; ***indicates $p < 0.001$.

ch acts as a filter When the filter becomes filled with (mainly red) blood cells red thrombus forms (**Figure 1A-D**). The integrin β2 on the white blood cells as shown by immunohistochemistry binds to factor X. Factor Xa is widely distributed on the fibrinogens/fibrins of filament-like network (**Figure 1E** and **1F**).

In this study, we report that there was expression of specific proteins in patients with symptomatic VTE, and the expression of these proteins was compared with VTE group patients and those with different risk factor groups (acute infection, malignancy, autoimmune diseases, trauma/surgery). In addition, the role of these proteins in the evaluation of risk for VTE is also assessed.

Methods

The subjects included patients with a definite diagnosis between March, 2011 and Feb, 2012 in Tongji Hospital of Tongji University. Patients were grouped by specific diseases based on the national standards by professionals, and the results were analyzed by statistic experts without knowledge of clinical status. Treatment decisions were not influenced by the findings of this research.

Patients and controls

A total of 1006 subjects (male = 53%; female = 47%; mean age = 67.40 ± 16.26) were enrolled from Departments of Cardiology, Internal Emergency, Oncology, Rheumatology, Surgical Emergency of Shanghai Tongji Hospital, and divided into six groups: the VTE group (within three months of onset, n = 72). The VTE group consisted of patients with DVT and/or PE, and the diagnosis was confirmed by imaging and the patients received anticoagulant therapy with low molecular heparin or warfarin orally. The acute infection group (n = 330) included patients with infections of respiratory tract (pneumonia or bronchitis, n = 168), urinary tract (n = 54), skin, soft-tissue (n = 25), intra-abdominal (gastrointestinal or hepatobiliary infections) (n = 64), or sepsis (no site identified) (n = 19). The patients received anti-infection and comprehensive therapy. The malignancy group (clinical stage III-IV, n = 144) included Lung cancer (n = 56), gastric cancer (n = 23), esophagus cancer (n = 12), rectum cancer (n = 14), pancreatic cancer (n = 4), hepatic cancer (n = 9), Breast cancer (n = 18), brain cancer (n = 8). 47 cancer patients received chemotherapy, and the others received comprehensive therapy including chemotherapy, radiotherapy, immunization therapy and treatment by Chinese herbs. The autoimmune diseases group (mild to moderate, n = 103) included rheumatoid arthritis (n = 39), systemic lupus erythematosus (n = 32), Sjogren's syndrome (n = 17), connective tissue disease (n = 15). They all received conventional immunoregulation and/or Chinese medicine treatments. The trauma/surgery group (n = 111) included 79 cases of several trauma (multiple injuries, n = 36;

head injury, n = 28; traumatic fractures, n = 15) and 32 surgical patients (cervical or lumbar vertebra surgery, n = 16; gastric cancer surgery, n = 5; intestinal cancer surgery, n = 11) general or local anesthesia time > 30min. The control group (non-risk factor group) included patients with atherosclerotic heart disease or/and hypertension (n = 246), but without clinically symptomatic VTE, acute infection, cancer, autoimmune diseases, trauma and recent surgical treatment were excluded.

Methods for detection

Levels of integrin β1, β2 and β3 in all individuals were detected and analyzed by EPICS XL-4 flow cytometry (Beckman-Coulter) using System II software. Fluorescent antibodies were provided by BD Company.

Patients were placed in a sitting position, and peripheral blood (2 ml) was collected from the median cubital vein and anti-coagulated with EDTA. After mixing, flow cytometry was done within two hours.

100 μl EDTA was added to each tube for anticoagulation. Isotype control was also included. Integrin β1 and integrin β2 were mixed with 20 μl mouse IgG1-PE, and integrin β3 was mixed with 20 μl mouse IgG2-PE. Then, 20 μl fluorescent antibody was added to above solution. After misce bene, incubation was done at room temperature in dark for 30 min. After addition of 500 μl hemolysin, incubation was done at 37°C for 30 min. Following washing, 500 μl sheath fluid was added and then detected by flow cytometry.

The standardized BECKMAN-COULTER fluorescent microspheres were used to adjust the PMT voltage, fluorescence compensation, sensitivity, and the detection protocol was determined. A total of 10000 cells were collected in each tube. The scattered plot of isotype control was used for gating at corresponding cells. Integrin β1 and integrin β2 gating were lymphocytes (**Figure 2A**), and integrin β3 gating was platelets (**Figure 2B**). According to the fluorescence intensity in each quadrant, the proportion of positive cells was calculated (%). Data were analyzed with SYSTEM-II software.

Statistical analysis

Continuous variables were expressed as means ± SD or medians (interquartile range), and categorical variables were expressed as frequencies (percentages). Control ranges of integrin positive cells were determined from control individuals. The control ranges of integrins β1 and β3 positive cells were calculated as the mean ± 2SD, and were 3.14 to 13.90% and 4.39 to 14.7%, respectively (**Table 1**). Using the 5th-95th percentiles, we determined control range of integrins β2 positivity (non-normally distributed) of 73.40 to 95.30 (**Table 1**). Integrin levels above the upper limit of the control range were considered positive, while levels below the upper limit of the control range were considered negative (**Table 1**).

Results and discussion

A total of 1006 inpatients were divided into: symptomatic VTE group, acute infection group, malignancy group, autoimmune diseases group, trauma/surgery group and control group. Expression of integrins was detected in these groups.

Compared with control group, the integrin β1 expression in VTE group and subjects with different risk factors (acute infection, malignancy and autoimmune diseases) increased markedly ($P < 0.001$, < 0.01). However, compared with control group, the integrin β1 expression in trauma/surgery group was not significantly different ($P > 0.05$, **Figure 3**).

Compared with control group, the integrin β2 expression in VTE group increased significantly ($P < 0.05$). Compared with control group, in different risk factor groups (acute infection, malignancy, autoimmune diseases and trauma/surgery), the integrin β2 expressions were not significantly different ($P > 0.05$, **Figure 3**).

Compared with control group, the integrin β3 expression in VTE group was significantly elevated ($P < 0.05$). However, the integrin β3 expressions in different risk factor groups (acute infection, malignancy, autoimmune diseases, trauma/surgery) were not significantly different ($P > 0.05$, **Figure 3**).

Table 2 shows that: Compared with integrin β1 negative individuals, the OR for VTE among integrin β1 positive individuals was 4.88 fold (95% CI: 2.69-8.83), which was higher than ORs in other groups. In groups with risk factors, the highest OR (OR: 3.33 fold; 95% CI: 2.01-5.50) was found in the malignancy group.

Table 3. Multiple-factor analysis of integrin β1, β2, β3 level in different groups

Groups	Variables	B	OR* (95% CI)
VTE	β1β2 series	1.49	4.44 (2.11-9.34)
	β2β3 series	1.79	6.04 (1.40-25.92)
	β1β3 series	3.10	22.27 (2.63-188.2)
	β1β2β3 series	2.36	10.65 (1.09-104.0)
	β1β2β3 parallel	1.93	6.90 (3.88-12.28)
Infection group	β1β2 series	0.84	2.32 (1.28-4.22)
	β2β3 series	1.54	4.67 (1.36-16.03)
	β1β3 series	2.52	12.47 (1.64-94.70)
	β1β2β3 series	1.66	5.30 (0.64-43.35)
	β1β2β3 parallel	1.18	3.28 (2.27-4.72)
Malignancy group	β1β2 series	0.84	2.31 (1.16-4.63)
	β2β3 series	1.79	6.04 (1.63-22.33)
	β1β3 series	3.00	20.26 (2.58-158.6)
	β1β2β3 series	2.66	14.39 (1.78-116.2)
	β1β2β3 parallel	1.06	2.90 (1.86-4.50)
Autoimmune disease group	β1β2 series	1.11	3.04 (1.48-6.24)
	β2β3 series	1.61	5.01 (1.22-20.43)
	β1β3 series	3.02	20.03 (2.54-167.1)
	β1β2β3 series	2.29	9.89 (1.09-89.66)
	β1β2β3 parallel	0.88	2.41 (1.48-3.94)
Trauma-surgical group	β1β2 series	-0.19	0.82 (0.31-2.15)
	β2β3 series	-0.30	0.73 (0.07-7.15)
	β1β3 series	-12.61	Small simple size
	β1β2β3 series	-12.61	Small simple size
	β1β2β3 parallel	0.22	1.25 (0.75-2.08)

Footnotes: * indicates VTE, INF, CAN, IMD, SUR vs. CONTROL. β1β3 series-positive population had the highest VTE risk, followed by β1β2β3 series-positive population, β2β3 series-positive population and β1β2 series-positive population. The OR value of the β1β3 series-positive population was 20.26 (95% CI: 2.58-158.6), 20.03 (95% CI: 2.54-167.1), 12.47 (95% CI: 1.64-94.7) in the malignancy group and autoimmune group, infection group, respectively.

Similarly, compared with integrin β2 negative individuals, the OR for VTE among integrin β2 positive individuals was 3.93 fold (95% CI: 2.18-7.09), which was higher than ORs in other groups. In groups with risk factors, the acute infection group had the highest OR (OR: 2.64 fold; 95% CI: 1.73-4.04). Compared with integrin β3 negative individuals, the OR for VTE among integrin β3 positive individuals was 7.18 fold (95% CI: 2.87-17.9), which was significantly higher than ORs in other groups. In groups with risk factors, the highest OR (OR: 4.25 fold; 95% CI: 1.79-10.04) was found in the malignancy group.

To screen the risk of VTE, combined indexes of integrins β1, β2 and β3 were adopted to investigate the impact of combined indexes on prediction of VTE onset.

Table 3 showed, β1 β2 β3 parallel positive people had 6.90 fold higher VTE risk than that of negative population (95% CI: 3.88-12 .28). The OR value for β1β3 series, β1β2β3 series, β2β3 series, β1β2 series in the VTE group was 22.27 (95% CI: 2.63-188.2), 10.65 (95% CI: 1.09-104.0), 6.04 (95% CI: 1.40-25.9), 4.44 (95% CI: 2.11-9.34), respectively. In the risk factor groups, the OR value of β1β2β3 parallel-positive population was 3.28 (95% CI: 2.27-4.72), 2.90 (95% CI: 1.86-4.50), 2.41 (95% CI: 1.45-3.94) in the infection group, malignancy group and autoimmune group, respectively. β1β3 series-positive population had the highest VTE risk, followed by β1β2β3 series-positive population, β2β3 series-positive population and β1β2 series-positive population. The OR value of the β1β3 series-positive population was 20.26 (95% CI: 2.58-158.6), 20.03 (95% CI: 2.54-167.1), 12.47 (95% CI: 1.64-94.7) in the malignancy group and autoimmune group, acute infection group, respectively. There was no significant increase in the trauma/surgery group.

The principal findings in this study are firstly that there is an increased expression of integrins β1, β2 and β3 in patients with VTE. Secondly, that in most patient groups traditionally considered at risk of VTE (infection, inflammation and malignancy) there was increased expression of β1 but not of β2 and β3. However this increased expression was not found in patients following trauma or surgery calling into question that such patients are at increased VTE risk in the absence of other factors such as concomitant infection.

Integrins are cell adhesion receptors, and they play an important role in the interaction be-

tween cells and extracellular matrix, and in cell-cell interactions [5]. Integrins are heterodimers consisting of non-covalently linked α and β transmembrane glycoprotein subunits. They consist of at least 18 α and 8 β subunits, producing 24 different heterodimers [6]. The α and β subunits separate from each other once the integrin is activated, and then the α subunit binds the ligand. The β1 subunit is expressed mainly on cell surface of lymphocytes, and its ligands consist of laminins, collagens, thrombospondin, vascular cell adhesion molecule 1 and fibronectin [7, 8]. The β2 subunit is distributed on cell surface of neutrophils and monocytes, and ligands for this subunit include fibrinogen, complement component iC3b, intracellular adhesion molecule-1, factor X and so on [9, 10]. The β3 subunit is observed on platelets, and this subunit binds fibrinogen, fibronectin, vitronectin von Willebrand factor and thrombospondin [11, 12].

Integrin β1 is mainly expressed on lymphocytes, and increased integrin β1 expression is related to the inflammation, thrombosis, homing of lymphocytes and metastasis of cancer cells. Integrin β2 is mainly distributed on neutrophils and monocytes, and increased integrin β2 expression is associated with inflammation. Integrin β3 is mainly expressed on platelets, and elevated integrin β3 expression suggests the platelet activation which is associated with platelet aggregation and thrombosis.

The study results showed that the expression of integrin β1, β2 and β3 increased significantly in VTE group, and integrin β1 elevated markedly in risk factor groups (acute infection, malignancy and autoimmune diseases), but that of integrin β2, β3 had no significant difference in all risk factor groups. This suggests that there was difference in the protein expression between VTE group and risk factor groups. The elevated integrin β2, β3 expression suggests neutrophils, monocytes and platelet activation which is a basic process in the inflammation and thrombosis. Thus, we speculate that risk factor groups have activation of lymphocytes immune cells, and VTE group are activation of lymphocytes、neutrophils both immune cells and platelets. Trauma/Surgery group who have no activation of immune cells and platelets may be not the "true" risk factor for VTE.

In the present study, the elevated expression of integrin β1, β2 and β3 in VTE group patients was highly consistent with the findings from immunohistochemistry of red thrombus in acute PE patients. In risk factor groups, those with acute infection, malignancy, autoimmune diseases have increased expression of integrin β1, but the integrin β2, β3 expression had no significant difference. This suggests that there is expression difference of core proteins of red thrombus between VTE group and risk factor groups (acute infection, malignancy or autoimmune diseases, trauma/surgery). In the screening of VTE patients, the increased expression of integrin β1 suggests the elevated risk for venous thrombosis and prevention against VTE should be done in these patients. The increased expression of integrin β1, β2 and β3 has a value in the clinical diagnosis of VTE. To detect the expression of integrin β1, β2 and β3 is helpful to diagnose VTE and screen risk people, thus, integrin β1, β2 and β3 may serve as new specific protein markers of VTE and risk people.

The current work is based on the previous studies on genomics [13], proteomics [4], bioinformatics and venous thrombosis core protein screened by immunohistochemistry [14, 15]. The present study aimed to verify the core protein in VTE group and risk factor groups. Due to the limitations of sample size in our study, further larger-size or multi-central studies on the normal range of the venous thrombosis core protein are still needed.

Conclusion

The significant increase in integrin β2, β3 expression is a marker differentiating the VTE group patients from the risk factor groups. Trauma/surgery alone may not be an independent risk factor for VTE.

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Disclosure of conflict of interest

None.

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