Prevalence and risk factors of postoperative venous thromboembolism in Cushing’s disease and establishment of a risk assessment model

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Abstract

Purpose: The incidence of venous thromboembolism (VTE) in Cushing's disease (CD) is about ten times higher than that in general population, which tends to be underestimated due to the missed detection of asymptomatic VTE events. VTE can occur at any stage of CD, mainly during the postoperative period. We aim to investigate the incidence and prothrombotic risk factors of postoperative VTE in CD patients and to further develop an assessment model to identify those at high risk of postoperative VTE events.

Methods: We performed a retrospective study in 82 CD patients by evaluating their clinical, hormonal, and coagulation parameters, as well as ultrasonography and pulmonary angio-CT when necessary.

Results: Nineteen patients (23.2%) developed VTE events, of which 14 developed VTE after endoscopic transsphenoidal surgery (ETS). The group of CD patients with postoperative VTE were elder ($p<0.001$), had more infection ($p<0.05$) and reduced mobility ($p<0.05$), higher HbA1c, and more severe impairment of glucose tolerance than those without. By using stepwise regression analysis, we obtained 4 independent risk factors for postoperative VTE: age, 2-h insulin in OGTT, current infection, and postoperative bedtime. Then a VTE risk assessment nomogram model was established to predict the patients at high risk of VTE. In this nomogram model, 70 patients (85.7%) were classified correctly, and area under the curve was 0.899 (95%CI, 0.787-0.999).

Conclusion: Advanced perioperative assessment needs to be taken to screen those with high VTE risks in CD patients. Moreover, physical movement and antithrombotic prophylaxis seems to be warranted during perioperative period.

Introduction

Endogenous Cushing's syndrome (CS) is a clinical state of sustained exposure to excess glucocorticoid that results from excessive adrenocorticotropic hormone (ACTH) production from the pituitary adenoma, ectopic ACTH secretion, or excessive autonomous secretion of cortisol from a hyperfunctioning adrenocortical tumor[1]. Up to 85% of ACTH-dependent CS cases were caused by ACTH- secreting pituitary adenomas (PAs), which were also referred as Cushing's disease (CD)[1]. Patients with CS have a high risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT)[2]. In CD patients, there remains some discrepancy regarding the incidence of VTE in previous studies, varying from 0 to 8.8% under the condition of prophylactic anticoagulant therapy[3–7], while it can be up to 20% in those without[3, 8–10]. Moreover, in most of these studies, only symptomatic VTE incident were confirmed by objective methods. In addition, numerous studies have revealed that asymptomatic VTE has a higher rate than symptomatic VTE in major surgeries, such as spine surgery[11]. Thus, it is of critical importance to evaluate the overall rate of VTE in CD patients who underwent transsphenoidal operation.

The onset of thromboembolism is a complex issue which mainly be concluded as a Virchow's triad: endothelial dysfunction, hypercoagulability, and stasis; which may act in synergy to increase the thromboembolic complications in hypercortisolism[12, 13]. Previous studies have identified some risk factors for postoperative thromboembolic events in CD patients, including inherited (such as hereditary thrombophilia like factor V Leiden, non-O blood groups) and environmental factors (reduced mobility, overt infections, invasive diagnostic procedures like inferior petrosal sinus sampling and surgery)[2, 5, 14, 15]. In addition, patients with CS also showed an impairment of the fibrinolytic system due to an excess of the fast-activating plasminogen activator inhibitor 1 (PAI-1)[16].

The Padua prediction score and Caprini risk assessment model are wildly used in medical and surgical inpatients to evaluate the risk of VTE, respectively[17]. However, whether they could make an accurate prediction of VTE in CD remained to be determined since they were not designed for these patients. Zilio M *et al.* identified six major independent risk factors for VTE in CS patients and established a CS-VTE score to predict the occurrence of VTE[5]. In their cohort, 94% patients can be classified correctly[5]. Nevertheless, whether this model could make an accurate prediction of VTE, both symptomatic and asymptomatic, in our cohort needs to be further verified.

In order to investigate the newly onset of postoperative VTE incidence rates in CD patients undergoing transsphenoidal surgery, we routinely performed the lower-limb ultrasonography and pulmonary angio-CT when necessary. Meanwhile, their clinical and hormonal data during active disease was also collected to further identify the major risk factors for postoperative VTE in CD patients by using a logistic multivariate regression analysis. In addition, we evaluated the accuracy of CS-VTE score, Pauda score and Caprini score in predicting postoperative VTE in our cohort; and further built an Huashan CD-VTE risk assessment model based on our data by using stepwise regression analysis and the least absolute shrinkage and selection operator (LASSO).

Patients And Methods

Study population

Eighty-two patients diagnosed with Cushing's disease (14 men and 68 women) aged 40.1 ± 12.8 years were recruited at Huashan Hospital affiliated to Shanghai Medical College, Fudan University from January 2019 to January 2020. This retrospective observation cohort study was approved by the Ethics Committee of Huashan hospital, Fudan University (ethical approval document number: KY2017-422). All patients were diagnosed and treated by Huashan Cushing multi-disciplinary team (MDT), including department of endocrinology, neurosurgery, pathology, and radiology, according to the current guidelines[18–20]. Cushing's disease was diagnosed on the basis of its characteristic clinical manifestation, standard hormone test results, and results of magnetic resonance imaging (MRI) or bilateral inferior petrosal sinus sampling (BIPSS)[18]. Total 26 patients received BIPSS in our cohort. All patients underwent endoscopic transsphenoidal surgery (ETS) and the final diagnosis of CD was histologically confirmed with the ACTH immunostaining by two senior pathologists in blinded fashion.

Clinical evaluation

All patients' clinical, ultrasonography, coagulation, and hormonal data was collected before ETS and within 1-week, 1 month, 3 months after ETS. Baseline clinical parameters were collected as follow: gender; age; body height and weight used to calculate body mass index (BMI); blood pressure; course of disease; smoking history; history of diabetes mellitus, hypertension, cardiovascular events, and current medications. Perioperative infections that needed antibiotics were also recorded. In addition, period of bedtime during active disease or after surgery due to some surgical complication like cerebrospinal fluid rhinorrhea was also collected for further analysis. Here in our study, we defined bedtime more than 3 days as reduced mobility. The presumed course of disease was estimated by the time from the appearance of symptoms likely to be related to hypercortisolism (i.e., weight gain, purple striae, increase in blood pressure, irregular menstruation, etc.) to the moment of evaluation.

Lower-limb Doppler ultrasonography was performed to screen VTE in 38 patients before surgery, and in 27 patients within 1-week post-surgery when their D-dimer showed an increasdd tendency compared to. In addition, pulmonary embolus (PE) was confirmed by pulmonary angio-CT when patients showed newly onset symptoms such as chest pain, coughing, shortness of breath, and decrease of oxygen saturation.

Laboratory tests

We tested blood glucose, insulin, and c-peptide during oral glucose tolerance test (OGTT); liver function; kidney function; lipid profile (includes plasma cholesterol, triglyceride, low-density lipoprotein and high-density lipoprotein); and coagulation profile. For serum hormones, we examined serum cortisol (timepoints included 8am, 4pm, and midnight; reference range: 7-10am, 6.20–19.4 μg/dl), plasma adrenocorticotropic hormone (ACTH) (7.2–63.3 pg/mL), 24-h urinary free cortisol (UFC, 30.15-129.13μg/24h urine), total thyroxine (TT_4), total triiodothyronine (TT_3), free thyroxine (FT_4), free triiodothyronine (FT_3), thyrotropin (TSH), insulin-like factor-1 (IGF-1). IGF-1 index was defined as the ratio of the measured value to the upper limit of the normal range (ULN) adjusted by age. Coagulation parameters included prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR), D-dimer (DDI), fibrinogen (FIB), and fibrinogen degradation products (FDP).

Construction of the predictive model

Stepwise selection was based on p-values, and the least absolute shrinkage and selection operator (LASSO) was used to select variables for modeling[21]. A variable's value with a $p < 0.05$ was regarded as significant and was retained. LASSO regression can compress the coefficients of the features via penalty function to obtain optimal constraint models; this practice has been used effectively to avoid over-fitting and co-linearity in classical analysis methods based on significance differences and also enhances the ability of a model to be generalized. Area under the ROC curve (AUC), with its 95% confidence limits, was estimated to describe the diagnostic discrimination of these parameters.

Statistical analysis

Data were presented as mean ± SD (or median with interquartile range) for continuous variables normally (or not normally) distributed, and as counts and proportions for categorical variables. The normal distribution of continuous variables was analyzed with the Kolmogorov-Sminov test. The student t test was used to analyze two groups of normally distributed continuous variables. Univariable analyses were performed using the Mann-Whitney U-test and Pearson's χ^2 test (where applicable). Univariate logistic regression analysis was used to identify the patients' clinical and biochemical parameters associated with VTE risk.

Statistical analysis was performed using the statistical package SPSS for Mac Ver. 26.0 (SPSS, Inc., Chicago, IL, USA), and graphs were prepared with Prism 8.0 (GraphPad) software. Significance was set as $P < 0.05$, which was based on two-tailed tests.

Results

As shown in **Table 1**, 82 patients (14 men and 68 women, aged 40.1±12.8 years) who diagnosed with CD were enrolled in our study. All patients received ETS and 74 patients (90.24%) relieved after surgery, of whom 71 patients had immediate remission and 3 patients showed delayed remission; whereas the remaining 8 patients didn't achieve remission. Nineteen patients (19/82, 23.17%) developed VTE, among which 5 cases were before surgery, 10 within 1-week after ETS, and the remaining 4 were within 40 days after ETS. After excluded those who developed VTE before surgery, the left 77 patients were then divided into two groups: postoperative VTE group (pVTE, n=14) and non-VTE group (non-pVTE, n=63). In the pVTE group, 2 patients had PE, while the remaining 12 were calf DVT events. Importantly, only 2 patients with PE showed symptoms of shortness of breath and decreased oxygen saturation post-surgery (3 and 14 days, respectively) and then diagnosed of coexistent DVT and PE, whereas the remaining 12 patients were all asymptomatic. Ten patients (71.4%) developed VTE within 1-week after surgery, and the remaining 4 were within 40 days postoperatively (14, 33, 35, and 40 days, respectively) (**Table 1**). Moreover, the postoperative mortality rate in our study was 1.22% (1/82), whose direct cause of death was brain hemorrhage and perioperative VTE events (diagnosed of DVT before surgery and DVT plus PE after surgery).

Baseline and clinical data for patients with postoperative VTE events

Patients' clinical, biochemical features, and comorbidities are summarized in **Table 2-1**. The mean age of patients in the pVTE group was 50 (range 37-58) versus 34 (range 29-43) in the non-pVTE group ($p<0.001$). Current infections and diabetes were more common among pVTE patients ($p<0.05$). Hematocrit, 2h insulin, and C-peptide in OGTT test, and alanine aminotransferase (ALT) levels were lower in the pVTE group ($p<0.05$); whereas HbA1c was higher ($p<0.05$).

Table 2-2 summarizes surgery-related data, hormonal, and coagulation data. The remission rate was 78.57% (11/14) in pVTE group. Though without statistical significance, a higher remission rate was observed in the non-pVTE group (59/63, 93.65%, p>0.05). It is shown that bed time, usually represented patients' statis status after surgery, was significantly longer in pVTE group than non-pVTE one (p0.01). However, we didn't observe statistical difference between groups when it comes to cerebrospinal fluid rhinorrhea rates, nadir cortisol levels after surgery within one week, as well as the post-surgery cortisol reduction value. In the meantime, no difference was observed regarding hormonal and coagulation parameters.

Correlations of postoperative VTE incident with clinical parameters in CD patients

Furthermore, we performed the correlation analysis to obtain the potent predictive parameters for VTE events in CD patients. As shown in **Table 3**, a strong positive correlation was found between VTE and age, course of disease, current infection, diabetes, blood urea nitrogen (BUN), HbA1c, postoperative bed time, and reduced mobility after surgery (defined as bed time3days). Meanwhile, VTE was negatively correlated with ALT, 2h insulin, and C-peptide in OGTT.

Accuracy of CS-VTE score, Pauda score, and Caprini score in predicting VTE in our cohort

When we verified the CS-VTE score raised by Zilio M and his colleagues, the accuracy was about 76.83%, with a sensitivity of 10.53% and a specificity of 96.83%; which indicated that this scoring system might not enough to make an accurate prediction of VTE in Chinese CD patients. We also evaluated our entire cohort with the Padua prediction score and Caprini risk assessment model, which are wildly used in non-surgical and surgical inpatients to evaluate the risk of VTE, respectively[17]. In the low-risk and high-risk group of Pauda score, 20.83% (15/72) and 40% (4/10) patients had VTE, with a sensitivity of 21.1% and a specificity of 90.5%. In the low-risk, medium risk, high risk and extremely high group of Caprini score, 14% (7/50), 26.32% (5/19), 50% (6/12) and 100% (n=1) patients had VTE, thus the sensitivity was 36.8% and the specificity was 91.9%. In conclusion, these risk models can partially predict VTE in CD patients, but far from satisfying.

Establishment of a venous thromboembolism risk assessment model

By using stepwise regression analysis, we obtained 4 independent risk factors for VTE: age, 2-h insulin in OGTT, current infection, and postoperative bedtime. The nomogram method of the postoperative risk assessment model was then shown in **Figure 1A**. When evaluating patients with this model, we determined the points of each risk factor and then did the vertical lines to get score for each item. After summing up the total points, we can get the risk of VTE. The AUC of this model was 0.899 (95% CI, 0.787-0.999) (**Figure 1B**).

Discussion

The present research demonstrates that CD patients in our single-center cohort study have a VTE incidence rate 10-fold higher than that in general population with matched age and sex[4]. Compared to controls, individuals that developed VTE after ETS were elder, who simultaneously have risk factors such as cardiovascular disease history, diabetes, unsatisfied blood pressure control, and postsurgical stasis. More importantly, asymptomatic VTE were much more common than symptomatic ones in our study, which raised the necessity to build a screening model for those with high VTE risk. In that case, after evaluating the prothrombotic risk factors for these patients, a risk assessment model was developed to identify those at higher risk of VTE.

Though numerous studies have investigated the incidence rates of VTE in CD patients, the results remained tremendous discrepancy, varying from 2–7.5% and up to 20%[3–10]. Moreover, considering the low incidence rate of CD in general population, currently there is no study exploring the prevalence of asymptomatic VTE. In a multicenter cohort study of CS patients, the investigator reported a high risk of post-operative VTE (3.4%), defined as risk within 3 months after surgery[22], was found in CD patients after transsphenoidal surgery[4]. In another study performed by Luca *et al*, 3 over 36 CD patients were diagnosed with VTE after submitted to transsphenoidal surgery, and thus the postoperative VTE incidence was ~ 7.5%[9]. In our study, up to 23.17% CD patients (19 out of 82 patients) were diagnosed with DVT with or without PE, which happened mainly within 40 days after surgery, especially within 1-week after surgery. The main discrepancy was that we screened symptomatic and asymptomatic VTE with ultrasonography in most CD patient. Once VTE was diagnosed, these patients received anticoagulant therapy, which could partially explain why the outcome tended to be less severe.

Our data highlight that VTE in CD patients can stem from different clinical, hormonal, and pathological coagulative situations in this cohort (Table 1–2). By using stepwise regression analysis, we obtained 4 independent risk factors for postoperative VTE: age, current infection, postoperative bedtime, and 2-h insulin in OGTT. Indeed, patients who developed VTE were on average older and had a higher prevalence of either severe infections or periods of reduced mobilization, both factors being well-known risk factors for VTE[23].

Four patients in our cohort had pneumonia, 3 with acute lung infections developed PE, while the remaining 1 was chronic pulmonary infection who developed DVT instead. Vice versa, 7 in 19 VTE patients had current infection (including lung and skin), while only 1 in 63 patients without VTE had current infection (skin infection). We presumed that acute active pulmonary infection played an important role in PE. A previous study by Chen YG *et al* found that the risk of developing DVT and PE were 1.78-fold and 1.98-fold respectively in patients with pneumococcal pneumonia compared to the control cohort with matched age, sex, and comorbidities[24]. Regarding to the underlying mechanism, local or systemic infection led to vessel wall damage and endothelial cell dysfunction, which further contributed to the hypercoagulation. We postulate that the control of preoperative infection is of great importance to reduce postoperative VTE complication.

In the context of the general population, surgery is an independent risk factor for VTE, especially in patients who are over 65 years old[25]. In a retrospective analysis evaluating patients who underwent surgeries of various lengths under general anesthesia (n = 1,432,855), the overall rate of post-operative VTE (within 30 days) was found to be 0.96%, with a positive association between length of surgery and VTE[26]. Though surgery is one of the main treatment options in CD, perioperative thrombotic risk, varies between 0 and 5.6%, is comparable to that observed after total hip or knee replacement under routine thromboprophylaxis[2]. Invasive operation like ETS can break the integrity of vascular endothelium, coupled with postoperative stasis or surgical complications (such as cerebrospinal fluid rhinorrhea) lead to circulation stasis, which can contribute to the VTE in CD patients. Thus, it is suggested that prophylactic use of anticoagulants, as well as enhancement of active and/or passive muscle movements in the lower body, are necessary in postoperative health care in these CD patients.

Our data also indicated that poorer diabetes and hypertension control were more common in VTE group than non-VTE one, which were manifested as higher HbA1c levels, lower 2h glucose-stimulated insulin and C-peptide level in OGTT, as well as more kinds of antihypertensive medication. Notably, it is well recognized that diabetes and hypertension impaires endothelial functions and intrigues systematic inflammation, which may further prompt the development of atherosclerosis[27]. In this situation, we presumed that diabetes and hypertension may play an important role in thrombosis.

The limitations of our study lied in the retrospective design, small size of cohort, and lack of normal controls. As our study showed, the prevalence of venous thromboembolism events in CD was higher than presumed. More than 20% patients had VTE and 4% had PE, the later one has been reckoned as the most lethal complication. Noteworthy, nowadays clinicians have shown increasingly awareness of VTE, and the prophylactic anticoagulant treatment was recommended in many previous studies, which could markedly reduce the prevalence of VTE[6]. Nonetheless, no guideline or common sense about the optimal dose and duration of prophylactic anticoagulation in CD has been put forward. Randomized prospective studies are warranted to investigate the accuracy of our prediction model and further establish the antithrombotic prophylaxis procedures.

Conclusions

Our study indicated that up to 23.17% patients diagnosed with CD developed DVT and/or PE, which mainly occurred within 40 days after surgery, especially within 1-week. After evaluating the prothrombotic risk factors for VTE in CD patients, a risk assessment model was developed to identify these patients at higher risk of VTE. Considering the high VTE incidence, it is essential to mobilize patients do lower limb exercise soon after surgery and encourage ambulation as early as possible[28]. Moreover, antithrombotic prophylaxis with heparin and/or warfarin seemed to be recommended in all CD patients undergoing ETS, particularly during the early postoperative period. Whereas for those with VTE risk factors, advanced perioperative assessment and management procedures need to be settled. Due to the size limitation of our cohort, studies performed in multicenter are needed to verified the prevalence and risk factors of VTE.

Moreover, our risk assessment model also needs to be validated prospectively in a larger cohort of CD patients.

Declarations

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Tables

Table 1: characteristics of VTE in the entire cohort

Patient No.	Gender	age	Time		VTE	Relevant risk factors
			(pre-/post-surgery)	day(s)		
1	F	63	Pre-	-	DVT	BIPSS, skin and connective tissue infection
2	F	52	Pre-	-	DVT+PE	Pulmonary infection with or without intracranial infection
3	F	50	Pre-	-	DVT	-
4	F	68	Pre-	-	DVT	Chronic pneumonia (after treatment)
5	F	49	Pre-	-	DVT	Skin fungal infection
6	F	41	Post-	40	DVT	-
7	M	19	Post-	14	DVT+PE	Pulmonary infection, papillary thyroid carcinoma
8	F	37	Post-	33	DVT	-
9	F	49	Post-	35	DVT	Hypertrophic obstructive cardiomyopathy, severe antral gastritis
10	F	45	Post-	3	DVT	Cerebral hemorrhage
11	F	58	Post-	2	DVT	-
12	F	58	Post-	6	DVT	-
13	F	57	Post-	4	DVT	-
14	F	50	Post-	3	DVT	-
15	F	36	Post-	1	DVT	-
16	F	58	Post-	2	DVT	-
17	F	59	Post-	3	DVT+PE	Pneumocystis pneumonia
18	F	55	Post-	5	DVT	-
19	M	65	Post-	4	DVT	Skin fungal infection

Table 2-1: Baseline clinical and biochemical data associated with postoperative VTE

	pVTE (n=14)	Non-pVTE (n=63)	*P* value
Sex (Male/female)	2/12	12/51	NS
Age (year)	50.00(37-58)	34(29-43)	**<0.001**
BMI (kg/m2)	26.50±4.25	25.54±4.06	NS
Course of disease (month)	77.14±72.72	43.62±56.27	NS
Comorbidities			
Current infection (yes)	3(36.84%)	1(1.59%)	**0.018**
Diabetes (yes)	10(71.43%)	23(36.51%)	**0.017**
Hypertension (yes)	12(85.71%)	45(71.43%)	NS
Course of diabetes (month)	16.46±34.70	8.05±22.04	NS
Course of hypertension (month)	59.21±64.20	23.09±46.05	NS
Kinds of antihypertensive drugs	1.86±1.35	1.48±1.38	NS
Hemoglobin (g/L)	134.93±22.80	145.11±17.22	NS
Hematocrit (%)	40.75±5.70	44.06±4.56	**0.022**
HbA1c (%)	7.22±1.26	6.26±1.10	**0.010**
2h glucose-stimulated insulin(mU/L)	37.40(9.40-80.60)	107.50(38.8-217.75)	**0.009**
2h glucose-stimulated C-peptide (ug/L)	8.84±5.26	15.01±9.78	**0.043**
ALT(U/L)	21(16-26)	26.5(15.25-36.75)	**0.033**

Table 2-2: Surgery-related data and baseline hormonal and coagulation data associated with postoperative VTE

	pVTE (n=14)	Non-pVTE (n=63)	*P* value
Cured after surgery	11/14 (78.57%)	59/63 (93.65%)	NS
CSF rhinorrhea	7/14(50%)	20/63(31.75%)	NS
Bed time (day)	5.57±2.14	4.10±1.75	**0.008**
Reduced mobility (bed time□3days)	11(78.57%)	34(53.97%)	NS
nadir cortisol after surgery (μg/dL)	3.92±5.67	2.47±2.97	NS
reduction of cortisol between pre-and post-surgery (pg/mL)	19.55±8.79	24.90±10.78	NS
8amF (μg/dL)	23.48±5.08	27.37±11.02	NS
0amF (μg/dL)	21.58±9.56	22.23±12.84	NS
8amACTH (pg/mL)	85.89±74.65	91.91±49.79	NS
0amACTH (pg/mL)	74.21±55.81	73.57±47.83	NS
24hUFC (μg)	293.44 (268.64-786.21)	482.1 (248.8-672.8)	NS
INR	0.88±0.04	0.89±0.05	NS
PT (s)	10.39±0.53	10.49±0.59	NS
APTT (s)	19.11±2.10	19.79±2.73	NS
FIB (g/L)	2.74±0.51	2.86±0.95	NS
D-D (FEUmg/L)	0.34 (0.19-0.48)	0.22 (0.19-0.34)	NS
TT (s)	18.99±1.10	18.19±2.40	NS
FDP (μg/ml)	2.47±0.74	2.39±0.60	NS

Table 3: Correlations of the postoperative VTE incident with clinical parameters in CD patients

	R value	*P* value
Age	0.307	0.001
Course of disease	0.200	0.040
Current infection	0.345	0.003
Diabetes	0.272	0.018
ALT	-0.205	0.033
BUN	0.242	0.013
HbA1c	0.270	0.013
2h glucose-stimulated insulin	-0.285	0.017
2h glucose-stimulated C-peptide	-0.245	0.040
Bed time	0.243	0.017
Reduced mobility	0.261	0.023
Course of hypertension	0.172	NS
Hematocrit	-0.182	NS
Na	-0.073	NS
Reduction of cortisol after surgery	-0.125	NS

Figures

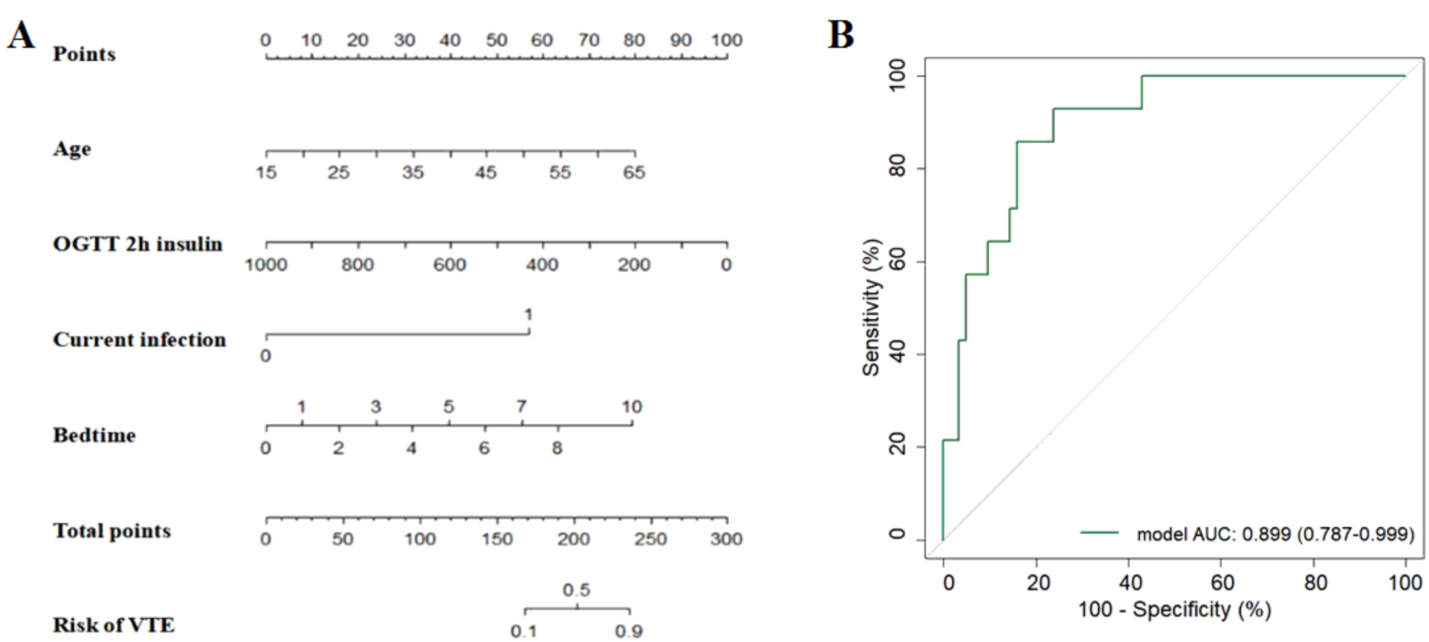

Figure 1

Nomogram for predicting the postoperative VTE risk in CD patients. (**A**) To use the nomogram for an individual patient, the points (top gridline) for each predictor variable are first assigned and the total points calculated. A vertical line from this value on the Total Points gridline then provides a probability for predicting VTE risk. The results of the binary variable are encoded as 0 and 1, representing the absence and presence of this symptom, respectively. (**B**) The area under curve (AUC) of this predictive model was 0.899 (95% CI, 0.787-0.999).