Original Article

Analysis of risk factors for early stent thrombosis in the Chinese population: A multicenter restrospective study

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BACKGROUND: The predictive scoring systems for early stent thrombosis (EST) remains blank in China. The study aims to evaluate the risk factors and conduct a prediction model of EST in the Chinese population.

METHODS: EST was defined as thrombosis that occurs within the first 30 days after primary percutaneous coronary intervention (PCI). Patients from ten Chinese hospitals diagnosed as stent thrombosis (ST) from January 2010 to December 2016 were retrospectively included as the study group. A control group (1 case:2 controls) was created by including patients without ST, major adverse cardiovascular events, or cerebrovascular events during follow-up. The present study evaluated 426 patients with single-vessel lesions and ultimately included 40 patients with EST and 80 control patients, who were included to identify factors that predicted EST and to develop a prediction scoring system. The other 171 patients without integrated 1:2 pair were used for external validation.

RESULTS: EST was independently associated with a low hemoglobin concentration (adjusted odds ratio [*OR*] 0.946, 95% confidence interval [95% *CI*] 0.901–0.993, *P*=0.026), a high pre-PCI Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (*OR* 1.166, 95% *CI* 1.049–1.297, *P*=0.004), and a DAPT (DAPT) duration of <30 days (*OR* 28.033, 95% *CI* 5.302–272.834, *P*<0.001). The simple EST prediction score provided an area under the curve (AUC) of 0.854 (95% *CI* 0.777–0.932, *P*<0.001) with 70.0% sensitivity and 90.0% specificity, and 0.742 (95% *CI* 0.649–0.835, *P*<0.001) with 54.5% sensitivity and 81.0% specificity for external validation dataset.

CONCLUSIONS: EST may be independently associated with DAPT discontinuation within 30 days, a low hemoglobin concentration, and a high SYNTAX score. The scoring system also has a good ability to predict the risk of EST and may be useful in the clinical setting.

KEYWORDS: Coronary heart disease; Stent thrombosis; Risk stratification; Predictive scoring system

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INTRODUCTION

Stent thrombosis (ST) is a rare complication of percutaneous coronary intervention (PCI) and is associated with high rates of morbidity and mortality. For example, patients who experience ST for the first time have in-hospital mortality rates of 5%–10% and 30-day mortality rates of 10%–25%.[1-4] The Academic Research Consortium has defined "definite" ST,[5] which can be classified as acute ST (within 24 hours), subacute ST (24 hours to 30 days), late ST (30–365 days), and very late ST (>365 days). Early ST (EST) is also defined as thrombosis that occurs within the first 30 days.[6] Although there are many biological, clinical, and angiographic features that can predict initial ST, there are limited data regarding the incidence, clinical presentation, and outcomes of EST. Previous studies have indicated that the incidence of EST is 10%–20% during long-term follow-ups, which highlights the need for a large multicenter study to evaluate the real-world outcomes of EST. Therefore, we aim to perform a retrospective analysis of risk factors and outcomes among Chinese patients with EST using a multicenter ST database.

METHODS

Study population and design

The present study's retrospective protocol was approved by the appropriate institutional ethics committees, which waived the requirement for informed consent.

We have previously constructed an electronic database that included 200 patients with angiographically confirmed ST who were treated in ten Chinese hospitals, where >1,000 PCI procedures were performed annually between January 2010 and December 2016. A control group (1 case:2 controls) was created by including patients without ST, major adverse cardiovascular events, or cerebrovascular events during follow-up. The cases and controls were matched according to the following criteria: (1) the same institution and (2) the operation was performed within one month before/after the PCI procedure. The present study evaluated 426 patients with single-vessel lesions and ultimately included 40 patients with EST and 80 control patients, who were included to identify factors that predicted EST and to develop a prediction scoring system. The other 171 patients without integrated 1:2 pair were used for external validation.

Definitions and data collection

Potential risk factors for EST were identified based on previous studies and our own clinical experience. Trained staff searched the patients' medical records to collect detailed data regarding demographic, laboratory, angiographic, medication, and procedural characteristics for the case and control groups, which were subsequently entered into an online data acquisition system.

Development and validation of an EST prediction scoring system

A scoring system for predicting EST was developed using each variable's partial regression coefficient. Each patient's total EST prediction score was calculated as the sum of each risk factor's value multiplied by its partial regression coefficient (the final equation is presented in the "EST prediction score" section). Partial regression coefficients were used instead of odds ratio (*OR*) to minimize the influence of the most powerful predictor(s). The model's goodness of fit was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the ROC curve (AUC) was calculated to evaluate the model's ability to predict the development of EST. The present study involved external validation using ROC curves for 171 unmatched patients. Good discriminative power was considered to be present when the AUC was >0.70.

Statistical analysis

Univariate conditional logistic regression analyses were performed to generate *OR*s and 95% confidence intervals (95% *CI*s) for each variable using SPSS software (version 22.0; IBM Corp., USA). Continuous variables were reported as mean±standard deviation and compared using univariate logistic regression analysis. Categorical variables were reported as number (percentage) and compared using univariate logistic regression analysis. Multivariable conditional logistic regression analysis was performed to identify independent risk factors for ST using significant variables from the univariate analyses ($P<0.1$). The optimal cut-off value for predicting EST was identified using ROC curve analysis based on the highest Youden's index value. Differences were considered statistically significant at *P*-values of <0.05.

RESULTS

Baseline clinical characteristics of EST patients

The baseline clinical characteristics of the EST and control groups, as well as the results of the univariate conditional logistic regression analyses, are shown in Table 1. The two groups had generally similar characteristics in terms of age, sex, and cardiovascular risk factors, including diabetes mellitus, hyperlipidemia,

smoking, and family history of premature coronary artery disease (all $P>0.1$). The EST group had a non-significantly higher proportion of hypertension (70.0% vs. 52.5%, $P=0.071$).

The laboratory and medication characteristics are also shown in Table 1. The EST group had a significantly high neutrophil-to-lymphocyte ratio ($P=0.019$), as well as significantly low value for hemoglobin ($P=0.003$), and high values for total bilirubin ($P=0.021$) and fasting blood glucose ($P=0.019$). The present study also considered the duration of dual antiplatelet therapy (DAPT), which was stopped within 30 days after the PCI procedure for 18 patients in the EST group and only three patients in the control group (*OR* 17.271, $P<0.001$). This result showed that the duration of DAPT influenced the occurrence of EST, and most patients who stopped DAPT within 30 days were not complying with the prescribed treatment.

The angiographic and procedural characteristics are also shown in Table 1, which revealed that the EST group had significantly higher PCI Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) scores ($P=0.001$). Qualitative comparative analysis revealed that, compared to the control group, the EST group had smaller minimal luminal diameters before the intervention and longer stent lengths, which indicated that the EST group had more severe lesions. There were no significant differences in the other predictors.

Independent predictors of EST

A multivariable conditional logistic regression model was used to identify independent predictors of EST using potential risk factors with univariate *P*-values of <0.1. The results revealed that EST was independently associated with a low hemoglobin concentration (adjusted *OR* 0.946, 95% *CI* 0.901–0.993, $P=0.026$), a high pre-PCI SYNTAX score (*OR* 1.166, 95% *CI* 1.049–1.297, $P=0.004$), and a DAPT duration of <30 days (*OR* 28.033, 95% *CI* 5.302–272.834, $P<0.001$). Thus, a

Table 1. Baseline clinical characteristics of EST group and control group

Variables	EST group (*n*=40)	Control group (*n*=80)	Univariate *OR*	*P*-value
Age, years, mean±SD	65.1±9.5	61.8±9.7	1.034	0.100
Male, *n* (%)	30 (75.0)	58 (72.5)	0.858	0.752
Hypertension, *n* (%)	25 (70.0)	42 (52.5)	2.146	0.071
Diabetes mellitus, *n* (%)	14 (35.0)	25 (31.3)	1.188	0.678
Hyperlipidemia, *n* (%)	11 (27.5)	17 (21.3)	1.542	0.394
Current smoker, *n* (%)	20 (50.0)	37 (46.3)	1.208	0.665
Family history of premature CAD, *n* (%)	2 (5.0)	4 (5.0)	1.000	1.000
Hemoglobin, g/L, mean±SD	131.6±15.2	140.0±14.3	0.950	0.003*
Activated partial thromboplatin time, seconds, mean±SD	31.6±7.6	31.7±6.2	0.995	0.900
NLR, mean±SD	4.6±2.8	3.3±2.4	1.205	0.019*
Total bilirubin, μmol/L, mean±SD	14.4±7.4	11.8±4.0	1.095	0.021*
HDL-C, mmol/L, mean±SD	1.1±0.2	1.1±0.3	1.337	0.698
LDL-C, mmol/L, mean±SD	2.8±1.2	2.5±0.8	1.407	0.113
Triglyceride, mmol/L, mean±SD	1.6±0.9	1.6±1.0	0.946	0.804
Cholesterol, mmol/L, mean±SD	4.4±1.3	4.1±1.0	1.263	0.228
Fasting blood glucose, mmol/L, mean±SD	7.8±3.8	6.4±2.0	1.263	0.019*
Duration of DAPT <30 days, *n* (%)	18 (45.0)	3 (3.8)	17.271	<0.001*
Duration of LMWH, *n* (%)				
Not use	20 (50.0)	52 (65.0)		0.060
≤3 days	11 (27.5)	12 (15.0)	14.448	0.019*
>3 days	9 (22.5)	16 (20.0)	9.156	0.086
Type of lesions[a], *n* (%)				
A+B1	2 (5.0)	3 (3.8)		0.505
B2	10 (25.0)	28 (35.0)	0.558	0.543
C	28 (70.0)	49 (61.3)	0.969	0.973
Bifurcation lesion, *n* (%)	17 (42.5)	29 (36.3)	1.281	0.519
Total occlusive lesion, *n* (%)	12 (30.0)	15 (18.8)	1.757	0.189
Pre-PCI SYNTAX score, mean±SD	17.0±10.3	10.3±7.2	1.097	0.001*
Pre-PCI reference vessel diameter, mm, mean±SD	2.7±0.4	2.8±0.6	0.638	0.260
MLD, mm, mean±SD				
Before intervention	0.5±0.5	0.7±0.5	0.496	0.073
After intervention	2.2±0.5	1.6±0.6	0.581	0.133
Luminal net gain, mm, mean±SD	1.6±0.7	1.6±0.6	1.038	0.898
Stent length, mm, mean±SD	32.9±13.7	28.8±11.7	1.032	0.076
MSD, mm, mean±SD	2.4±0.4	2.6±0.5	0.494	0.102
Length of stent, mm, mean±SD	2.8±0.4	3.0±0.5	0.580	0.245
Post-dilation, *n* (%)	23 (57.5)	46 (57.5)	1.000	1.000

EST: early stent thrombosis; SD: standard deviation; *OR*: odds ratio; CAD: coronary artery disease; NLR: neutrophil-to-lymphocyte ratio; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; DAPT: dual antiplatelet therapy; LMWH: low-molecular-weight heparin; PCI: percutaneous coronary intervention; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; MLD: minimum lumen diameter; MSD: minimal stent diameter; *$P<0.05$; [a]: classification of coronary artery disease in AHA/ACC.

DAPT duration of <30 days had the greatest influence on the risk of EST (Table 2).

EST prediction score

A simple EST prediction score was calculated based on the risk score for each variable minus the minimum risk value:

Total score=hemoglobin (g/L)×(–0.055)+pre-PCI SYNTAX score×(0.154)+DAPT duration of <30 days (0/1)×(3.638)–the minimum risk value (160×[−0.055] +0×0.154+0×3.638).

The ROC curve for identifying the optimal EST score cut-off value (4.83 points) is shown in Figure 1. In the internal validation dataset, this score provided an AUC of 0.854 (95% *CI* 0.777–0.932, *P*<0.001) with 70.0% sensitivity and 90.0% specificity. In the external validation dataset, the same cut-off value provided an AUC of 0.742 (95% *CI* 0.649–0.835, *P*<0.001) with 54.5% sensitivity and 81.0% specificity.

DISCUSSION

The new generation of drug-eluting stents has significantly reduced the incidence of restenosis, relative to bare metal stents, although the increased risk of ST has become a major problem. A previous study[7] has revealed that early ST and late ST have different risk factors, which can be generally categorized as patient-related factors, disease-related factors, procedure-/stent-related factors, and drug-related factors. The main causes of EST are incomplete stent apposition and inadequate stent expansion. In our study, we found that EST was independently associated with a low hemoglobin concentration, a high SYNTAX score, and early cessation of DAPT.

The SYNTAX score is a measurement of coronary artery disease extent and severity, which is a strong predictor of death, myocardial infarction, target vessel revascularization, and major adverse cardiac events after PCI in various patient populations.[8-10] However, there is limited research regarding the ability of the SYNTAX score to predict EST. The present study revealed that the EST group had significantly higher SYNTAX scores before the PCI procedure (17.0±10.3 vs. 10.3±7.2). In addition, the risk of ST seemed to increase proportionately with coronary artery disease extent and severity. These findings may be explained by the fact that a high SYNTAX score includes most risk factors associated with ST (e.g., longer, more diffuse, and/or more calcified lesions). Moreover, the presence of complex and extensive coronary artery disease increases

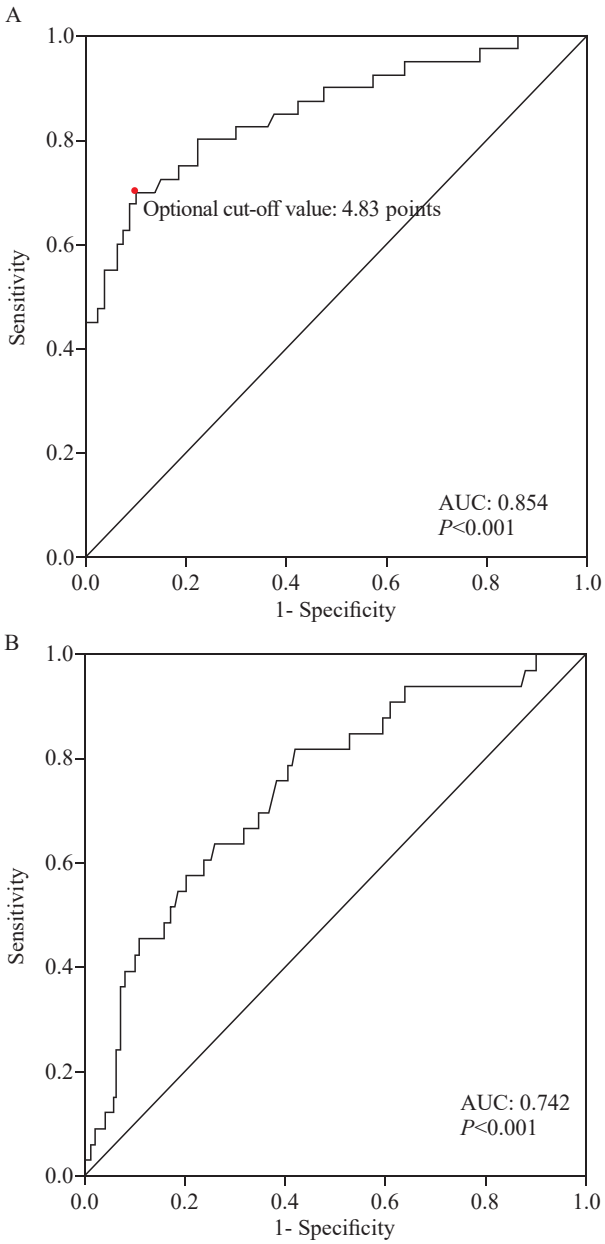

Figure 1. Receiver operating characteristic curve analysis of EST scoring prediction system. A: internal validation; B: external validation.

Table 2. Independent predictors of EST

Variables	*β*	Adjusted *OR* (95% *CI*)	Adjusted *P*-value
Hemoglobin	–0.055	0.946 (0.901–0.993)	0.026
Duration of DAPT <30 days	3.638	28.033 (5.302–272.834)	<0.001
Pre-PCI SYNTAX score	0.154	1.166 (1.049–1.297)	0.004

EST: early stent thrombosis; *OR*: odds ratio; *CI*: confidence interval; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

the likelihood of requiring multiple and longer stents, which would be intuitively related to a proportionally higher risk of ST.

The choice of anticoagulants is also very important in this setting, and all of our patients were pre-treated using unfractionated heparin, acetylsalicylic acid, and clopidogrel. The currently recommended DAPT regimen for coronary heart disease is acetylsalicylic acid plus a P2Y12 receptor inhibitor (ticagrelor or clopidogrel) for longer than six months. However, patients may choose to discontinue antiplatelet therapy for various reasons, which can be categorized as discontinuation according to the physician's orders, discontinuation because of an impending invasive procedure (≤14 days), and discontinuation due to bleeding events or poor compliance. However, platelet activation and aggregation are the main pathogeneses of coronary heart disease, especially in patients with acute coronary syndrome (who should receive antiplatelet therapy for >12 months), and these processes are upregulated after discontinuation of antiplatelet therapy. Therefore, our findings confirm that early discontinuation of DAPT is a risk factor for EST.[11-13]

Anemia or a low hemoglobin concentration among patients with coronary heart disease or PCI is associated with continuous myocardial ischemia (induced by low blood oxygen), older age, more comorbidities, poor cardiac and renal functions, and more complex coronary lesions. Approximately 10%–40% of patients who undergo PCI have anemia, which is a dual risk factor for bleeding and the recurrence of coronary heart disease. A previous study[14] has confirmed that preoperative anemia was an independent predictor of major adverse cardiac events (death at 30 days and one year, as well as myocardial infarction recurrence after PCI), and the risk of major adverse cardiac events increased with increasing anemia severity. A preliminary study also revealed that there was a U-shaped relationship between hemoglobin concentration and the prognosis after acute coronary syndrome emergencies among patients who underwent PCI, with the lowest two-year mortality rate observed at hemoglobin concentrations of 140–160 g/L. Moreover, almost 50% of the patients who died (predominantly cardiogenic deaths) had baseline hemoglobin concentrations of <129 g/L. The present study failed to detect a clear relationship between anemia and ST, although patients with anemia after PCI may have an increased risk of ST, given their increased risks of ST-induced recurrent myocardial infarction and death. The present study also revealed that the independent risk factors for EST were DAPT discontinuation within 30 days, a high preoperative SYNTAX score, and a low hemoglobin concentration, which may increase the risk of ST and other events despite not fulfilling the diagnostic criteria for anemia.

Limitations

The present study has several limitations. First, it involved a retrospective analysis of a highly selected patient cohort. Second, we could not evaluate intraluminal imaging data, which previous studies have used to identify stent malapposition, stent underexpansion, and marginal dissection. Finally, our EST scoring system was developed using data from patients who underwent PCI in a single vessel, which indicated that the scoring system must be validated among patients with more complicated lesions.

CONCLUSIONS

The present study reveals that EST is independently associated with DAPT discontinuation within 30 days, a low hemoglobin concentration, and a high pre-PCI SYNTAX score. The scoring system also has a good ability to predict the risk of EST and may be useful in the clinical setting.

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Contributors: All authors made an individual contribution to the writing of the article, including design, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, and manuscript editing.

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