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ORIGINAL RESEARCH

The Important Role of Preoperative D-Dimer in Constrictive Pericarditis

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Background: The impact of coagulation indicators on postoperative outcomes of patients with constrictive pericarditis undergoing pericardiectomy has been poorly investigated. This study aimed to assess the prognostic role of preoperative coagulation indicators in these patients.
Methods: We retrospectively included 158 patients with constrictive pericarditis undergoing pericardiectomy. The diagnostic values of coagulation indicators for postoperative complications were evaluated by ROC curves. Patients were divided into two groups according to the cutoff value calculated by ROC curve. Postoperative outcomes were compared between the two groups. Logistic regression analysis was performed to identify risk factors of postoperative complications.
Results: ROC curve showed that among different coagulation indicators, preoperative D-dimer (DD) level could effectively identify patients with postoperative complications (AUC 0.771, 95% CI 0.696–0.847, $P < 0.001$). Patients were divided into the low DD group and the high DD group. The comparison of postoperative outcomes suggested that high preoperative DD level was significantly associated with longer durations of vasoactive agents using ($P = 0.018$), intubation ($P = 0.020$), ICU stay ($P = 0.008$), chest drainage ($P=0.004$) and hospital stay ($P = 0.002$). Multivariable analysis showed that high preoperative DD level was the independent risk factor of postoperative complications (OR 6.892, 95% CI 2.604–18.235, $P < 0.001$).
Conclusion: High preoperative DD level was significantly linked to poor postoperative outcomes and could provide an effective prediction ability for postoperative complications in patients with constrictive pericarditis.
Keywords: constrictive pericarditis, D-dimer, postoperative complications, outcomes

Introduction

Constrictive pericarditis is a rare and severe disease caused by thickened and inelastic pericardium.[1] The etiology of constrictive pericarditis is various including idiopathic, viral, prior cardiac surgery, history of radiotherapy, malignancy and trauma, whereas the most common cause remains to be tuberculosis, especially in developing countries.[2–4] The prognosis for constrictive pericarditis is poor, and in most cases conservative treatment only provides temporary relief of symptoms.[5] Pericardiectomy is a definitive treatment option, but surgical resection of pericardium carries a high risk of postoperative mortality with reported rate up to 17.6%.[6–9]

Given the difficulty of predicting precise prognosis in constrictive pericarditis, some easily accessible indicators, such as laboratory indicators, should be considered as predictors for a more accurate prognosis evaluation. Coagulation indicators are frequently screened preoperatively and taken into account during perioperative planning. Abnormal coagulation profiles could result in adverse postoperative outcomes.[10,11] Among coagulation indicators, D-dimer has received growing attention especially and is commonly associated with various clinical settings such as inflammation, pneumonia, cancer, septicemia and surgery.[12] Nevertheless, it is unclear about the effect of coagulation on postoperative outcomes of constrictive pericarditis. This study aimed to assess whether preoperative coagulation indicators had an impact on postoperative outcomes in constrictive pericarditis, thereby helping surgeons to screen out high-risk patients for early intervention.

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Methods

Patients and Data Collection

The study protocol was approved by the Institutional Review Board of Hangzhou Red Cross Hospital (No. 2023140), and considering the nature of the retrospective study, written patient informed consent was waived. A total of 158 patients with clinically diagnosed constrictive pericarditis who underwent radical pericardiectomy at Hangzhou Red Cross Hospital between November 2012 and October 2023 were enrolled in this study. Patients with incomplete coagulation test results were not eligible.

The diagnosis of constrictive pericarditis was primarily based on clinical symptom, cardiac imaging and central venous pressure (CVP).[13] Cardiac imaging examinations mainly included echocardiography and chest enhanced computed tomography. Cardiac magnetic resonance was also performed to confirm the diagnosis in some cases. The etiology of constrictive pericarditis was evaluated by pathologic examination and pathogen detection on resected pericardial tissue. All the information was obtained from the database of the Hangzhou Red Cross Hospital. The coagulation test results were collected within one week prior to operating surgery, including D-dimer (DD), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), thrombin time (TT) and fibrinogen (FBG).

Surgery and Postoperative Outcomes

All included patients underwent radical pericardiectomy by median sternotomy without the use of cardiopulmonary bypass. The anterolateral pericardium between the two phrenic nerves, the pericardium from superior vena cava-right atrium junction to inferior vena cava-right atrium junction, the pericardium on the great arteries and the basal pericardium over the diaphragmatic surface were all included in the extent of pericardiectomy.[14]

The primary outcome was postoperative complications which were defined as the comorbidities occurring after pericardiectomy. The major postoperative complications included cardiac complications, pulmonary complications, acute liver or kidney injury and deep vein thrombosis. Cardiac complications included low cardiac output and arrhythmia. The definition of low cardiac output included decrease in the cardiac index to <2.0 liters per minute per square meter of body-surface area and a systolic blood pressure of <90 mmHg with signs of tissue hypoperfusion.[15] Pulmonary complications included pneumonia, acute respiratory failure, atelectasis and pulmonary embolism. Other postoperative outcomes that were recorded included duration of intensive care unit (ICU) stay, intubation, vasoactive agents using, chest drainage, hospital stay and in-hospital mortality.

Statistical Analysis

The receiver operating characteristic (ROC) curve was constructed to analyze the correlation between coagulation indicators and postoperative complications, with the calculation of the area under curve (AUC). The cutoff value of coagulation indicator was determined by the ROC curve. The studied patients were divided into two groups according to the cutoff value. The proportions of categorical variables were assessed by Pearson's chi-square test, corrected chi-square test or Fisher's exact test. The comparison of continuous variables was tested by the Student's *t*-test or Mann–Whitney *U*-test. Univariable and multivariable logistic regression models were performed to calculate the odds ratio (OR) and 95% confidence interval (CI). Variables with P <0.05 in univariable analysis were entered into a multivariable analysis. These analyses were conducted using R version 4.2.1 (https://www.r-project.org/) and SPSS software (version 24.0, IBM SPSS Inc. United States). The statistical significance was considered as a P <0.05 on two sides.

Results

ROC Curve

A total of 158 patients were available for analysis, and postoperative complications were reported in 59 (37.3%) patients, with cardiac complications in 34 (21.5%) patients, pulmonary complications in 20 (12.7%) patients, acute liver or kidney injury in 14 (8.9%) patients and deep vein thrombosis in 4 (2.5%) patients (Table 1).

ROC curve analyses were performed to determine the correlation between coagulation indicators and postoperative complications. As shown in Figure 1A, preoperative DD level could effectively identify patients with postoperative

Table 1 Postoperative Complications After Pericardiectomy

Variables	N	Percentage
Total	59	37.3%
Cardiac complications	34	21.5%
Low cardiac output	27	17.0%
Atrial fibrillation	6	3.8%
Ventricular fibrillation	2	1.3%
Pulmonary complications	20	12.7%
Pneumonia	16	10.1%
Acute respiratory failure	4	2.5%
Atelectasis	3	1.9%
Pulmonary embolism	1	0.6%
Acute liver or kidney injury	14	8.9%
Acute liver injury	9	5.7%
Acute kidney injury	8	5.1%
Deep vein thrombosis	4	2.5%

complications from the studied population (AUC 0.771, 95% CI 0.696–0.847, P < 0.001). The value of the remaining indicators in identifying postoperative complications was not significant, with P = 0.658 for APTT, P = 0.082 for PT, P = 0.076 for INR, P = 0.896 for TT and P = 0.587 for FBG (Figure 1B–F).

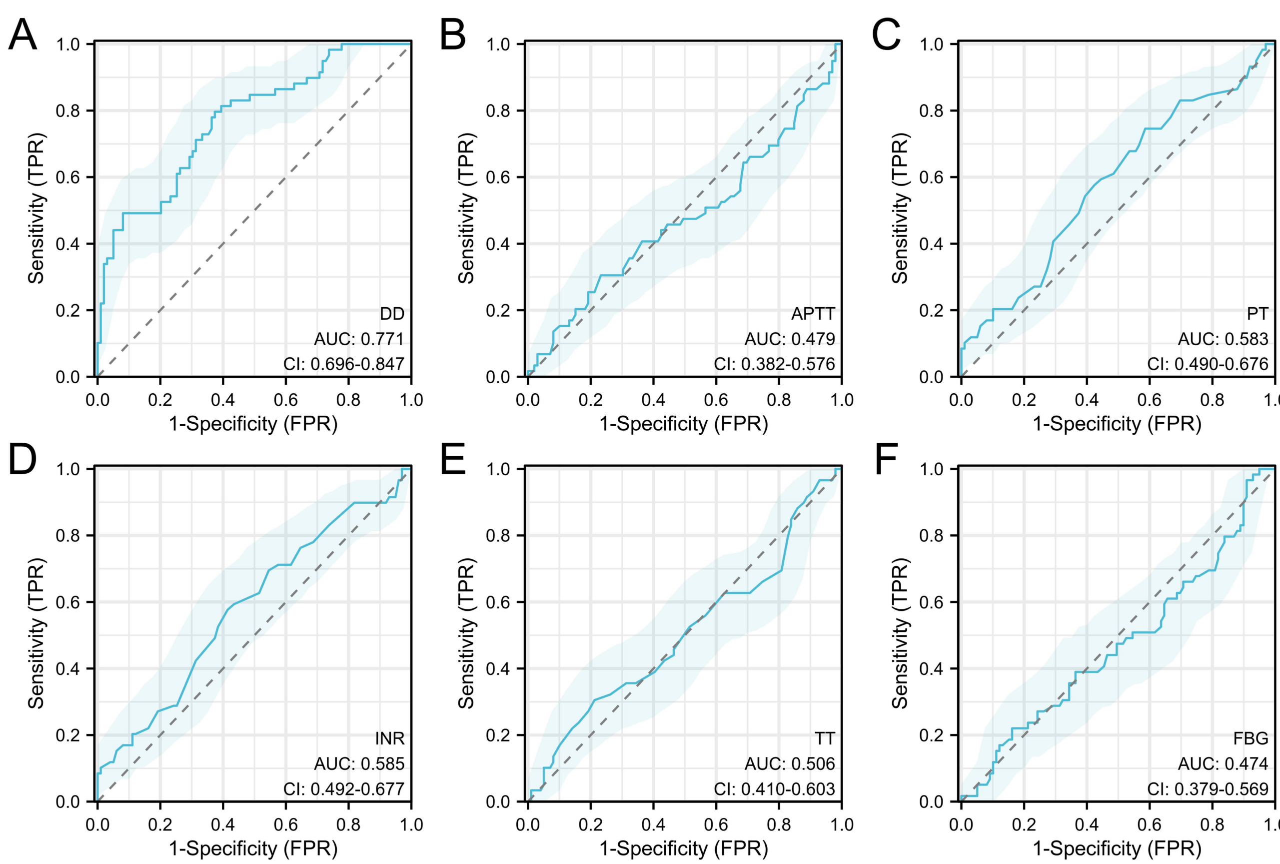

Figure 1 Analysis of the diagnostic value of coagulation indicators for postoperative complications. (**A**) ROC curve analysis of the diagnostic value of DD; (**B**) ROC curve analysis of the diagnostic value of APTT; (**C**) ROC curve analysis of the diagnostic value of PT; (**D**) ROC curve analysis of the diagnostic value of INR; (**E**) ROC curve analysis of the diagnostic value of TT; (**F**) ROC curve analysis of the diagnostic value of FBG.

Abbreviations: DD, d-dimer; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; TT, thrombin time; FBG, fibrinogen.

The results of ROC curve analyses showed that preoperative DD level also had diagnostic value for different types of postoperative complications (Figure 2), including cardiac complications (AUC 0.733, 95% CI 0.639–0.828, P < 0.001), pulmonary complications (AUC 0.739, 95% CI 0.617–0.861, P=0.001) and deep vein thrombosis (AUC 0.945, 95% CI 0.906–0.984, P = 0.002), but the diagnostic value for acute liver or kidney injury was not significant (AUC 0.655, 95% CI 0.510–0.800, P = 0.056).

Baseline Characteristics

In the studied population, a cut-off point of preoperative DD level was established at 2085.5 ug/L from the ROC curve, with a sensitivity of 79.7%, specificity of 62.6% and Youden index of 0.423. According to the cut-off value, 74 (46.8%) patients were assigned to the low DD group and 84 (53.2%) were assigned to the high DD group. The preoperative baseline characteristics of the two groups were presented in Table 2. Compared to the low DD group, a higher proportion of patients in the high DD group had tuberculosis as the etiology of constrictive pericarditis (95.2% vs 85.1%, P = 0.031). Inflammatory indicators such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also higher in the high DD group (P < 0.001 and P = 0.001, respectively). In the high DD group, the levels of platelets (P = 0.015) and international normalized ratio (INR) (P < 0.001) were higher than the low DD group. Prothrombin time (PT) was longer in the high DD group (P < 0.001). In addition, pericardium was thicker in the high DD group than in the low DD group (P < 0.001). In terms of comorbidities, patients in the high DD group had a higher rate of diabetes (P = 0.013), while other comorbidities were not significantly different between the two groups.

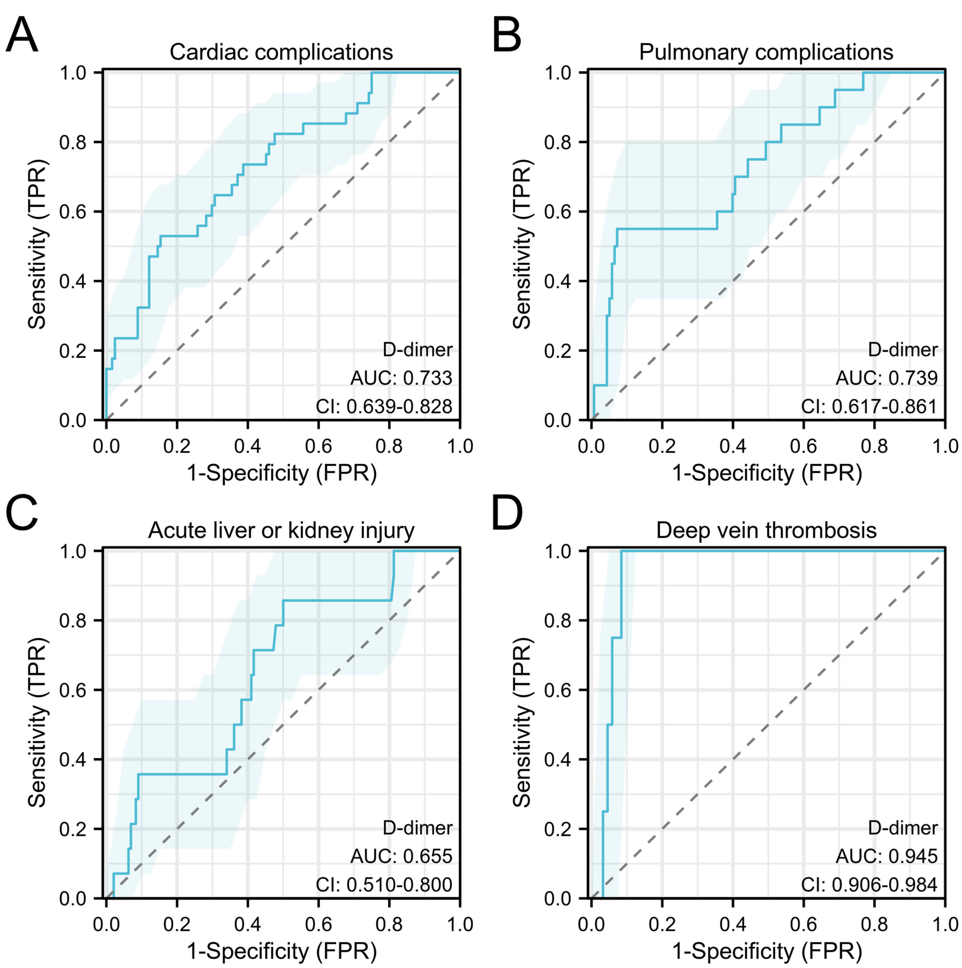

Figure 2 Analysis of the diagnostic value of D-dimer for different postoperative complications. (**A**) ROC curve analysis of the diagnostic value for cardiac complications; (**B**) ROC curve analysis of the diagnostic value for pulmonary complications; (**C**) ROC curve analysis of the diagnostic value for acute liver or kidney injury; (**D**) ROC curve analysis of the diagnostic value for deep vein thrombosis.

Table 2 Preoperative Baseline Characteristics of the Patients

Variables	Low DD Group (N=74)	High DD Group (N=84)	P value
Gender			0.958
Male	57 (77.0%)	65 (77.4%)	
Female	17 (23.0%)	19 (22.6%)	
Age, years	58 (18–79)	61 (16–83)	0.791
Etiology			0.031
Tuberculosis	63 (85.1%)	80 (95.2%)	
Idiopathic	11 (14.9%)	4 (4.8%)	
Smoking			0.093
Never	36 (48.6%)	55 (65.5%)	
Former	23 (31.1%)	16 (19.0%)	
Current	15 (20.3%)	13 (15.5%)	
Alcohol drinking			0.323
Never	50 (67.6%)	65 (77.4%)	
Former	8 (10.8%)	8 (9.5%)	
Current	16 (21.6%)	11 (13.1%)	
BMI, kg/m^2	21.5 (16.3–33.1)	21.4 (14.9–31.6)	0.206
NYHA functional class			0.692
I	3 (4.1%)	4 (4.8%)	
II	37 (50.0%)	34 (40.5%)	
III	32 (43.2%)	43 (51.2%)	
IV	2 (2.7%)	3 (3.6%)	
Hypertension	16 (21.6%)	15 (17.9%)	0.552
Diabetes	11 (14.9%)	3 (3.6%)	0.013
Atrial fibrillation	7 (9.5%)	15 (18.1%)	0.121
COPD	0 (0%)	3 (3.6%)	0.290
HIV	0 (0%)	0 (0%)	/
CHD	4 (5.4%)	5 (6.0%)	1.000
PVD	2 (2.7%)	5 (6.0%)	0.546
Stroke	0 (0%)	2 (2.4%)	0.499
DVT	2 (2.7%)	8 (9.5%)	0.153
Pericardial calcification	10 (13.5%)	20 (23.8%)	0.100
Pericardial thickness, mm	8.6 (3.4–18.4)	10.1 (4.0–22.0)	<0.001
CVP, cmH_2O	25.3 (13.0–40.0)	27.0 (14.0–50.0)	0.066
LVEF, %	58.4 (46.0–75.2)	59.1 (42.0–78.0)	0.976
Platelets, 10^9/L	134.5 (71–321)	160 (77–383)	0.015
APTT, sec	30.0 (20.3–40.3)	28.9 (21.7–46.9)	0.292
PT, sec	12.6 (9.5–15.7)	13.5 (10.8–16.6)	<0.001
INR	1.07 (0.87–1.31)	1.13 (0.93–1.40)	<0.001
TT, sec	16.7 (13.2–23.0)	16.8 (13.3–21.5)	0.280
FBG, mg/dL	342 (145–527)	357 (169–570)	0.497
CRP, mg/L	12.1 (0.8–71.5)	21.9 (1.0–86.4)	<0.001
ESR, mm/h	21.5 (2.0–90.0)	36.0 (2.0–129.0)	0.001
BNP, pg/mL	175 (15–786)	199 (21–961)	0.089

Notes: Values presented as N (percentage) for categorical variables and median (range) for continuous variables.

Abbreviations: DD, d-dimer; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; CHD, coronary heart disease; PVD, peripheral vascular disease; DVT, deep vein thrombosis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; LVEF, left ventricular ejection fraction (measured on echocardiogram); APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; TT, thrombin time; FBG, fibrinogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BNP, brain natriuretic peptide.

Postoperative Outcomes

Table 3 presents the results of the comparison of postoperative outcomes. Postoperative brain natriuretic peptide (BNP) level was higher in the high DD group than in the low DD group (P = 0.024). The frequency of postoperative complications was significantly higher in the high DD group (56.0% vs 16.2%, P < 0.001). The durations of vasoactive agents using, intubation and ICU stay were significantly longer in the high DD group (P = 0.018, 0.020 and 0.008, respectively). Longer durations of chest drainage and hospital stay were also observed in the high DD group (P = 0.004 and 0.002, respectively). One patient died in the high DD group, but the difference from the low DD group was not significant.

To further clarify the independent prognostic factors, we assessed the correlation between clinical characteristics and postoperative complications of the patients. The results of univariable and multivariable analyses were presented in Supplemental Table 1. Multivariable analysis showed that high preoperative DD level was the independent risk factor of postoperative complications (OR 6.892, 95% CI 2.604–18.235, P < 0.001) (Table 4).

Discussion

In this retrospective study, we employed a cohort in a single medical database with numerous clinical variables including coagulation indicators, and presented the results of ROC curves to determine the predictive value of coagulation indicators for postoperative complications. Preoperative DD level had a potential diagnostic value for postoperative complications and was significantly associated with postoperative outcomes among the patients with constrictive pericarditis receiving pericardiectomy. These results could provide some reference value to surgeons in identifying high-risk patients preoperatively.

In majority of cases, constrictive pericarditis is chronic, progressive and life-threatening, and tuberculosis is still the major cause.[16] In our study, more than 90% of patients were attributed to tuberculosis, especially in the high DD group. Surgery remains the only effective approach for relieving pericardial constriction but was accompanied with high risk of complications and mortality. Several previous studies have analyzed perioperative characteristics of patients undergoing

Table 3 Comparison of Postoperative Outcomes

Variables	Low DD Group (N=74)	High DD Group (N=84)	P value
CVP, cmH_2O	13.0 (3.0–28.0)	14.0 (2.0–32.0)	0.063
BNP, pg/mL	190 (27–803)	247 (25–1553)	0.024
ICU stay*, days	2 (0–10)	2 (0–11)	0.008
Intubation, h	19.5 (0–212)	21 (0–232)	0.020
Duration of vasoactive agents, h	0 (0–231)	13 (0–161)	0.018
Complications	12 (16.2%)	47 (56.0%)	<0.001
Duration of chest drainage, days	10 (4–27)	13 (4–52)	0.004
Hospital stay, days	15 (8–31)	18 (7–60)	0.002
In-hospital mortality	0 (0.0%)	1 (1.2%)	1.000

Notes: Values presented as median (range) for continuous variables and N (percentage) for categorical variables. *The average ± standard deviation of ICU stay (days) was 2.3±1.8 and 3.1±2.2 in low DD group and high DD group, respectively.
Abbreviations: DD, d-dimer; CVP, central venous pressure; BNP, brain natriuretic peptide; ICU, intensive care unit.

Table 4 Effect of Preoperative DD Level on Postoperative Complications

Groups	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	P value	OR	95% CI	P value
Low DD group	1	/	/	1	/	/
High DD group	6.563	3.090–13.942	< 0.001	6.892	2.604–18.235	< 0.001

Abbreviations: DD, d-dimer; OR, odds ratio; CI, confidence interval.

pericardiectomy and identified some meaningful risk factors such as preoperative functional class, CVP, pulmonary artery pressure, intraoperative fluid infusion rate and extent of resection.[17–20] In addition, the use of cardiopulmonary bypass was also associated with poor postoperative outcomes.[21,22] However, it has remained unknown about the effect of coagulation indicators on the postoperative outcomes.

Among coagulation indicators including DD, APTT, PT, INR, TT and FBG, we found the specific role of preoperative DD level in evaluating postoperative outcomes in constrictive pericarditis. DD has been broadly employed in the diagnostic assessment of suspected venous thromboembolism and aortic syndrome.[23] Moreover, elevated preoperative DD level could independently predict major complications and act as an independent prognostic factor for overall survival and recurrence free survival in patients with malignant diseases.[24–26] Previous studies also suggested that increased DD value was observed in virus and tuberculosis infected patients and was associated with the severity of diseases.[27,28] However, the relationship between DD and treatment outcomes in inflammatory diseases remains to be further explored.

Our study divided included patients into two groups according to the cutoff value of preoperative DD level. By comparing the baseline characteristics, we observed that patients in the high DD group had higher level of CRP and ESR than those in the low DD group, which could be explained by the higher proportion of patients with tuberculosis in the high DD group, but other important inflammatory parameters such as IL-6 were not evaluated in our study. This finding was consistent with a previous study and suggested that DD could be perceived as a measure of the inflammatory burden.[29] Reactive thrombocytosis has already been described in the context of inflammatory conditions.[30] Therefore, in patients with high DD, a significantly higher platelet count was also detected in this work. Interestingly, the levels of PT and INR were higher in the high DD group than in the low DD group, but the differences were not necessarily clinically significant.

Furthermore, we should also emphasize that significantly longer durations of postoperative vasoactive agents using, intubation and ICU stay were observed in patients with high preoperative DD level. Similarly, Hui Lian et al analyzed 8813 old patients admitted to ICU and found that DD level at ICU admission was strongly correlated with ventilation time in the old population.[31] The rise in DD was shown to be associated with endothelial dysfunction and fibrin accumulating in the alveoli.[32] Therefore, it was reasonable that high DD level led to longer durations of postoperative vasoactive agents using and intubation, which could be also a rational explanation for the association between high DD level and longer ICU stay. Our study further added preliminary evidence that high DD level was an independent risk factor for postoperative complications by univariable and multivariable analyses. These results highlighted the possibly of more severe clinical presentation in patients with high DD level.

Certain limitations relevant to this study should be acknowledged. First, because of the retrospective and single-center study design, the generalizability of our results is limited. Second, the sample size in this study is relatively small due to the low prevalence of constrictive pericarditis, so studies with larger sample size are needed to confirm the results. Third, the mechanisms of the link between DD and postoperative outcomes cannot be explicated in this study. Finally, only preoperative DD value is available in this dataset, which prevents us from having information on DD kinetics during the course of constrictive pericarditis.

Conclusion

Our study identified preoperative DD level as a diagnostic factor for postoperative complications, including cardiac complications, pulmonary complications and deep vein thrombosis. High preoperative DD level was significantly linked to poor postoperative outcomes and was an independent predictor of postoperative complications. These results suggested that DD could add useful clue for the risk stratification of patients with constrictive pericarditis undergoing pericardiectomy.

Abbreviations

DD, d-dimer; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; TT, thrombin time; FBG, fibrinogen; ROC, receiver operating characteristic; AUC, area under curve; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of Hangzhou Red Cross Hospital (No. 2023140). Because of the retrospective nature of the study and without any specific intervention, the informed consent has been agreed to be waived. The data were maintained with confidentiality. The present study complied with the Declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests in this work.

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