Predictors of post-operative cardiovascular complications for Behçet's disease with pre-operative immunosuppressive therapy

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Abstract

Objective

Patients with Behçet's disease (BD) with cardiovascular involvement often have more post-operative complications in correcting the pathology by surgical means. This study aims to explore the benefits of pre-operative immunosuppressive therapy, predict complications using inflammatory biomarkers, and evaluate optimal surgery timing.

Methods

This retrospective study analysed predictors of post-operative complications in BD patients who underwent cardiovascular surgery with perioperative immunosuppressive therapy at Guangdong Provincial People's Hospital from 2012 to 2024.

Results

In-hospital complications were lower in patients who received pre-operative immunosuppressive therapy (9% vs. 58.8%, $p<0.001$). Rheumatoid factor (RF, hazard ratio [HR] 1.088; 95% confidence interval [CI], 0.998–1.187; $p=0.056$), platelet-to-lymphocyte ratio (PLR, HR 1.004; 95% CI, 1.000–1.008; $p=0.075$), and neutrophil-to-lymphocyte ratio (NLR, HR 1.065; 95% CI, 1.002–1.133; $p=0.045$) were identified as independent risk factors for post-operative complications, while pre-operative immunosuppressive therapy (HR 0.206; 95% CI, 0.061–0.693; $p=0.011$) was a protective factor. The area under the curve (AUC) for the receiver operating characteristic curve for four or more positive biomarkers was 0.849.

Conclusion

Pre-operative immunosuppressive therapy is vital for BD patients. Monitoring inflammatory biomarkers helps identify the best timing for surgery and reduces complications.

Key words

Behcet's disease, immunosuppressive therapy, inflammatory biomarker

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Introduction

Behçet's disease (BD) is a rare multisystem inflammatory disorder with an unclear pathogenesis. According to a systematic autopsy study from Japan, up to 16.5% of BD patients have cardiac involvement (1), primarily manifesting as aortic regurgitation, aortic sinus aneurysm, coronary artery aneurysm, intracardiac thrombus, and endocardial or myocardial fibrosis (2). Although cardiac involvement is relatively uncommon, inflammation and tissue fragility caused by BD in periaortic tissues significantly increase the risk of post-operative complications, such as paravalvular leakage, BD recurrence requiring reoperation, and other adverse outcomes.

Numerous studies have suggested that perioperative immunosuppressive therapy (IST) can reduce post-operative complications and reoperation (3-5). A study demonstrated that post-operative IST was an independent protective factor for reducing paravalvular leakage after surgery (HR 0.38, 95% CI 0.17–0.89, p=0.025) (6). Most studies agree that pre-operative IST can reduce post-operative complications. However, considering that long-term IST increases infection and surgical risk, evaluating the effectiveness of IST and the optimal timing of surgical intervention requires further research.

Several biomarkers have been proposed to assess the activity and severity of inflammation. The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have been widely used in diabetes, hypertension, autoimmune diseases, and malignancies (7, 8). Elevated NLR, caused by either neutrophilia or lymphopenia, indicates active inflammation. NLR can be used to assess the inflammatory state in BD patients (9). Similarly, PLR and NLR are considered to have higher sensitivity and are often used to evaluate BD activity (10, 11). Additionally, MPV has been applied in assessing the activity of BD, which is higher in the BD group compared to those without but lower in stable BD patients compared with flare BD patients (12). A study on inflammation biomarkers in BD has shown that NLR is an independent predictor of inflammation, with PLR and MPV differing significantly between groups with varying disease severity (113).

Future research on BD focuses on accessible biomarkers for diagnosis, monitoring, and prognosis. However, studies on cardiovascular complications, particularly in patients receiving pre-operative IST combined with surgery, are limited. Most research on single markers has shown limited predictive value, and there is a lack of studies assessing the effectiveness of pre-operative immunosuppressive therapy and optimal surgery timing. More research is needed to improve treatment and outcomes.

Methods

Clinical data

A retrospective analysis was conducted on BD patients who underwent cardiovascular surgeries in Guangdong Provincial People's Hospital from 2012 to 2024. Two patients underwent a second cardiac surgery in our hospital due to paravalvular leakage during follow-up. A total of 50 cardiovascular surgeries were divided into two groups based on whether received pre-operative IST: 33 surgeries in the IST group and 17 in the non-IST group. Demographic characteristics, clinical features, surgical data, laboratory tests, and clinical outcomes were retrospectively collected for 48 patients across 50 surgeries using electronic medical records. This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (approval no: KY2024-044). Written informed consent was obtained from the patients.

Post-operative complications were defined as death or any of the following confirmed by echocardiography or coronary angiography: ventricular septal dissection, aneurysm (with or without rupture), thrombosis, paravalvular leakage, paravalvular abscess, infective endocarditis, prosthetic material infection, sepsis, acute BD recurrence, or valve prolapse. Follow-up data included death, cardiovascular reoperation, and the complications above.

Diagnostic data

Forty-three patients met the International Criteria for Behçet's Disease

(ICBD) (14) and the revised criteria established by the Behçet's Disease Research Committee of Japan (15). The remaining seven patients did not present with typical symptoms or signs of BD upon admission. However, intraoperative biopsy revealed neutrophil and mononuclear infiltration, endothelial loss, and fibrin deposition, confirming Behçet's vasculitis.
Patients with suspected BD-related cardiovascular involvement were evaluated by a multidisciplinary team, including cardiac surgeons, rheumatologists, echocardiographers, radiologists, and pathologists, using echocardiographic, surgical, and pathological findings.

Surgery and pre-operative IST
A median sternotomy was performed, and various procedures, including valve and aortic replacements, cardiac mass resection, coronary fistula repair, and concomitant valve surgeries, were conducted under hypothermic cardiopulmonary bypass.
IST use was adjusted based on inflammatory markers and clinical presentation. IST was tapered off one day before surgery, and all patients received post-operative IST.

Statistical analysis
Statistical analyses were performed using SPSS 26.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation and categorical variables as frequencies and percentages. The two-sample t-test or Mann-Whitney U-test was applied for continuous variables, while the chi-square test or Fisher's exact test was used for categorical data. Kaplan-Meier curves analysed post-operative complication probabilities.
Multivariate Cox regression identified risk factors for complications, and receiver operating characteristic (ROC) curve analysis in RStudio assessed the predictive efficacy of pre-operative inflammatory biomarkers. A *p*-value of less than 0.05 was deemed significant.

Results

Characteristics of BD patients
Thirty-one patients (62%) were male, and the mean age at first surgery was 38.98±10.1 years. Seven cases (14%) were initially misdiagnosed. A comparison between patients with and without pre-operative IST showed no significant differences in age at diagnosis (41.36±12.5 *vs.* 37.63±7.93, *p*=0.65), age at surgery (41.79±12.60 *vs.* 39.07±8.58, *p*=0.85), male proportion (64.7% *vs.* 60.6%, *p*=0.78), left ventricular ejection fraction (LVEF, 57.07±9.38 *vs.* 55.85±9.86%, *p*=0.93), left ventricular end-diastolic diameter (LVEDd, 59.86±9.36 *vs.* 61.22±8.72 mm, *p*=0.90), left ventricular end-systolic diameter (LVESd, 41.57±8.32 *vs.* 42.96±8.57 mm, *p*=0.93), interventricular septal thickness (IVD, 9.66±1.73 *vs.* 9.78±1.49 mm, *p*=0.24), or ascending aortic diameter (AAO, 34.79±7.89 *vs.* 34.56±7.22 mm, *p*=0.31) (Table I).
The IST group had significantly lower ESR (20.33±28.09 *vs.* 40.50±26.82 mm/h, *p*=0.04) and rheumatoid factor (RF, 9.46±4.02 *vs.* 14.57±6.32 IU/mL, *p*=0.004). There were no significant differences in PLR (131.75±55.57 *vs.* 156.65±156.70, *p*=0.56) or MPV (10.70±1.38 *vs.* 10.59±1.29 fL, *p*=0.71). However, NLR was significantly higher in the IST group (7.06±10.66 *vs.* 2.61±1.84, *p*=0.028) (Table I).
Among all patients, aortic valve replacement (AVR) was performed in 45 cases (90%), including 42 cases (93.3%) with mechanical prostheses, and aortic root replacement (Bentall procedure) was performed in 22 cases (44%). There were no significant differences between the IST and non-IST groups in the proportion of AVR (93.9% *vs.* 82.4%, *p*=0.43) or Bentall procedures (51.5% *vs.* 29.4%, *p*=0.14). Four patients had coronary artery bypass grafting (8%), two patients had coronary fistula repair (4%), and two patients had Cabrol procedures (4%). There were no significant differences in cardiopulmonary bypass (CPB) time (182.57±97.81 *vs.* 235.81±107.10 minutes, *p*=0.20), aortic cross-clamp (ACC) time (115.50±54.35 *vs.* 161.04±76.70 minutes, *p*=0.054), or post-operative intensive care unit (ICU) stay (7.21±10.41 *vs.* 7.7±9.85 days, *p*=0.99).
Twelve patients (24%) had in-hospital complications, including one in-hospital death (2%) and one case of paravalvular leakage (PVL) (2%). Two patients (4%) with severe pulmonary infections were transferred to local hospitals for further treatment. The IST group had fewer in-hospital complications (9.1% *vs.* 58.8%, *p*<0.001). There were no significant differences in the post-operative PVL (3% *vs.* 0%, *p*=1), sepsis (5.9% *vs.* 6.1%, *p*=1), or thrombosis (6.1% *vs.* 5.9%, *p*=1).
The mean follow-up duration was 31.63±25.46 months. During follow-up, six patients (12%) died, three patients (6%) had paravalvular leakage, two patients (4%) had BD relapse and three patients (6%) underwent reoperations. The IST and non-IST groups had no significant difference in all-time mortality (5.88% *vs.* 18.2%, *p*=0.40) and PVL (11.7% *vs.* 6%, *p*=0.88).

Biomarkers associated with post-operative complications
Among all patients, 21 (42%) had post-operative complications. Compared with those without complications, group with complications had higher levels of ESR (39.11±35.69 *vs.* 17.91±18.36, *p*=0.063), CRP (39.41±12.15 *vs.* 8.53±1.04, *p*=0.007), PLR (191.68±184.21 *vs.* 114.07±46.02, *p*=0.038), and RF (14.22±6.06 *vs.* 8.85±3.45, *p*=0.003). MPV (10.43±1.30 *vs.* 10.79±1.32, *p*=0.27) and NLR (8.67±12.55 *vs.* 3.08±2.93, *p*=0.093) showed no significant difference, although NLR tended to be higher in the group with complications. These findings indicate that patients with post-operative complications were in an active inflammatory state pre-operatively, which negatively impacted surgical outcomes (Table II).
Among patients who received pre-operative IST, the complication group had higher levels of ESR (29.75±44.53 *vs.* 15.43±16.52, *p*=1), RF (11.6±5.47 *vs.* 8.44±2.73, *p*=0.09), NLR (15.92±12.91 *vs.* 3.34±2.91, *p*<0.01), PLR (255.99±262.66 *vs.* 113.79±45.08, *p*=0.07), and CRP (59.29±62.15 *vs.* 11.11±22.28, *p*<0.01), while MPV was lower (9.95±0.69 *vs.* 10.83±1.28, *p*=0.06). CRP and NLR showed statistically significant differences (Fig. 1, Supplementary Fig. S1).
Univariate analysis included diagnos-

Table I. Clinical data of patients with Behcet's disease.

Variable	All (n=50)	Without IST (n=17)	With IST (n=33)	*p*-value
Age (years)				
Diagnosed age	37.96 ± 9.81	41.36 ± 12.5	37.63 ± 7.93	0.65
First surgery age	38.98 ± 10.13	41.79 ± 12.60	39.07 ± 8.58	0.85
Male	31 (62%)	11 (64.7%)	20 (60.6%)	0.78
Missed diagnosis	7 (14%)	7 (41.2%)	0	<0.001
Smoke	1 (2%)	0	1 (2%)	1
Hypertension	7 (14%)	3 (17.6%)	4 (12.1%)	0.918
Diabetes	2 (4%)	1 (5.8%)	1 (3%)	1
Involvement patterns				
Mucocutaneous involvement	39 (78%)	11 (64.7%)	28 (84.8%)	0.21
Articular involvement	25 (50%)	10 (58.8%)	15 (45.5%)	0.37
Vascular involvement	20 (40%)	8 (47.1%)	12 (36.4%)	0.47
Ocular involvement	7 (14%)	2 (11.7%)	5 (15.2%)	0.74
Pathergy test	9 (18%)	2 (11.7%)	7 (21.2%)	0.66
Inflammatory biomarkers				
Neutrophils(10^9/L)	7.06 ± 7.08	5.20 ± 2.93	8.01 ± 8.35	0.19
Lymphocytes(10^9/L)	1.97 ± 0.85	2.06 ± 0.63	1.93 ± 0.95	0.60
ESR(mm/h)	24.41 ± 27.40	40.50 ± 26.82	20.33 ± 28.09	0.04
RF(IU/mL)	11.12 ± 5.48	14.57 ± 6.32	9.46 ± 4.02	0.004
CRP(mg/L)	22.34 ± 37.85	21.55 ± 32.25	22.36 ± 41.40	0.70
PLR	139.17 ± 120.81	131.75 ± 55.57	156.65 ± 156.70	0.56
NLR	5.45 ± 8.28	2.61 ± 1.84	7.06 ± 10.66	0.028
MPV(fL)	10.64 ± 1.32	10.70 ± 1.38	10.59 ± 1.29	0.71
Immunosuppressive medication				
Glucocorticoids	33 (66%)	/	33 (100%)	/
Thalidomide	6 (12%)	/	6 (18.2%)	/
Cyclophosphamide	6 (12%)	/	6 (18.2%)	/
Hydroxychloroquine	6 (12%)	/	6 (18.2%)	/
Pre-operative echocardiography				
LVEF (%)	57.27 ± 9.81	57.07 ± 9.38	55.85 ± 9.86	0.93
LVEDd (mm)	60.11 ± 8.90	59.86 ± 9.36	61.22 ± 8.72	0.90
LVESd (mm)	41.76 ± 8.76	41.57 ± 8.32	42.96 ± 8.57	0.93
IVD (mm)	8.73 ± 3.29	9.66 ± 1.73	9.78 ± 1.49	0.24
AAO (mm)	31.22 ± 12.65	34.79 ± 7.89	34.56 ± 7.22	0.31
Infective endocarditis	6(12%)2(11.8%)	4(12.1%)>0.99		
Operation				
Aortic valve replacement	45 (90%)	14 (82.4%)	31 (93.9%)	0.43
Mechanical valve	42 (93.3%)	13 (76.5%)	29 (87.9%)	>0.99
Aortic root replacement (Bentall)	22 (44%)	5 (29.4%)	17 (51.5%)	0.14
Cardiac mass resection	1 (2%)	1 (5.9%)	0	0.34
CABG	4 (8%)	1 (5.9%)	3 (9.1%)	>0.99
Coronary artery fistula repair	2 (4%)	0	2 (6.1%)	0.54
Cabrol procedure	2 (4%)	0	2 (6.1%)	0.54
CPB time (min)	217.26 ± 101.21	182.57 ± 97.81	235.81 ± 107.10	0.20
ACC time (min)	145.26 ± 69.51	115.50 ± 54.35	161.04 ± 76.70	0.054
Post-operative ICU stay (days)	7.14 ± 9.19	7.21 ± 10.41	7.7 ± 9.85	0.99
In-hospital complication	12 (24%)	9 (52.9%)	3 (9.1%)	<0.001
Death	1 (2%)	0	1 (3%)	>0.99
Sepsis	3 (6%)	1 (5.9%)	2 (6.1%)	>0.99
Paravalvular leakage	1 (2%)	1 (5.9%)	0	0.34
Thrombosis	2 (4%)	1 (5.9%)	1 (3%)	>0.99
Follow-up				
Death	7 (14%)	1 (5.9%)	6 (18.8%)	0.40
BD relapse	2 (4%)	2 (12%)	0	0.04
Paravalvular leakage	4 (6%)	2 (12%)	2 (6.3%)	0.88
Reoperation	3 (6%)	1 (5.9%)	2 (6.3%)	>0.99
Complication time (months)	18.78 ± 18.97	10.19 ± 12.53	23.21 ± 20.33	0.016
Follow-up time (months)	31.63 ± 25.46	41.81 ± 30.25	26.40 ± 21.25	0.073

IST: immunosuppressive therapy; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; CRP: C-reactive protein; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; IVD: interventricular septum dimension; AAO: ascending aorta; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; ACC: aortic cross-clamp; ICU: intensive care unit.

tic age, first surgery age, missed diagnosis, concurrent infective endocarditis, IST, and inflammatory biomarkers, different type of operation. The results showed RF (HR 1.22; 95% CI 1.065–1.398; *p*=0.006) as a risk factor for post-operative complications and IST (HR 0.058; 95% CI 0.006–0.6; *p*=0.017) as a protective factor.

Table II. Univariate and multivariate Cox regression analysis of post-operative complications.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Diagnosed age (years)	0.763	0.419, 1.392	0.378			
First surgery age (years)	1.332	0.738, 2.402	0.341			
ESR (mm/h)	1.000	0.961, 1.040	0.984			
RF (IU/mL)	1.22	1.065, 1.398	0.006	1.126	1.023, 1.238	0.015
CRP (mg/L)	1.039	0.981, 1.101	0.196	1.015	1.000, 1.030	0.047
PLR	0.999	0.980, 1.018	0.920			
NLR	1.079	0.947, 1.229	0.252	1.065	1.002, 1.133	0.034
MPV (fL)	0.843	0.458, 1.552	0.584			
Infective endocarditis	6.558	0.679, 63.940	0.106			
Pre-op IST	0.058	0.006, 0.6	0.017	0.139	0.039, 0.487	0.002
Cabrol	27.308	1.879, 396.781	0.015	18.771	1.820, 193.611	0.014
Aortic root replacement (Bentall)	0.593	0.136, 2.583	0.486			
CABG	0.555	0.056, 5.528	0.615			

ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; CRP: c-reactive protein; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; Pre-op IST: pre-operative immunosuppressive therapy.

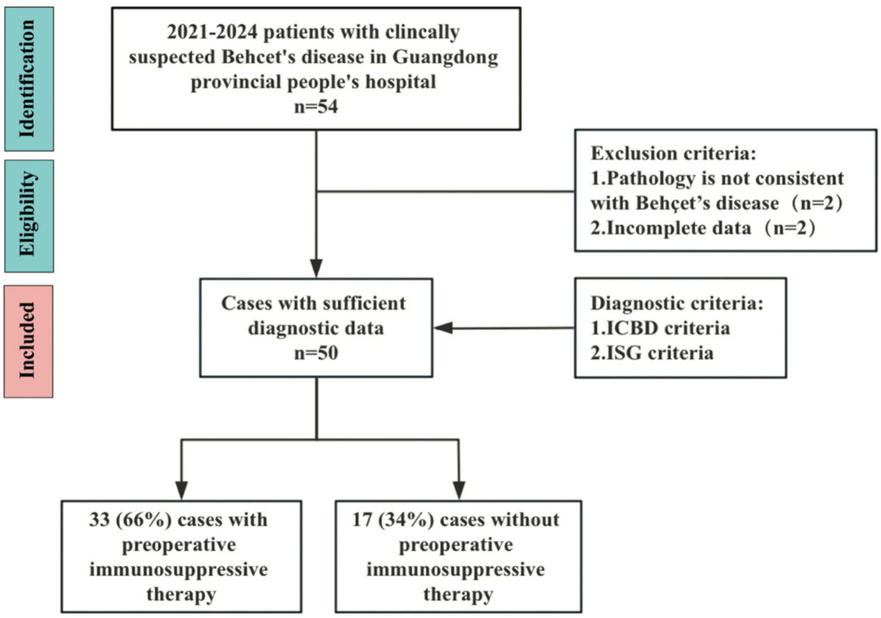

Fig. 1. Flow diagram of the inclusive and exclusive process of the study.

Multivariate Cox regression analysis further indicated that RF (hazard ratio 1.088; 95% CI 0.998–1.187; p=0.056), PLR (HR 1.004; 95% CI 1.000–1.008; p=0.075), and NLR (HR 1.065; 95% CI 1.002–1.133; p=0.045) were independent risk factors. Meanwhile, IST (HR 0.206; 95% CI 0.061–0.693; p=0.011) was an independent protective factor.

Predictive biomarkers

We analysed PLR, NLR, RF, and MPV using the ROC curve. The PLR cut-off value was 95.62, with a sensitivity of 90.5%, specificity of 41.4%, and AUC of 0.673. The NLR cut-off value was 2.04, with a sensitivity of 81%, a specificity of 48.3%, and an AUC of 0.64. The cut-off value for MPV was 9.39, with a sensitivity of 28.6%, a specificity of 93.1%, and an AUC of 0.592. The cut-off value for pre-operative RF was 9.5, with a sensitivity of 66.7%, a specificity of 88.9%, and an AUC of 0.745 (Suppl. Tables S1, S2).

We developed a clinical model using various variables. In this model, inflammatory biomarkers (excluding MPV) are negative if below the cut-off value, while MPV is negative only if it exceeds. ROC curve analysis indicated that having four or more positive biomarkers resulted in an AUC of 0.849, with a sensitivity of 90.5% and a specificity of 79.3% (Fig. 2).

Survival analysis

The K-M survival analysis compares post-operative complications survival probability based on grouping RF, ESR, CRP, PLR, NLR, and MPV by their respective cut-off values. The results showed that patients with high RF (p<0.001), PLR (p=0.026), NLR (p=0.027), CRP (p=0.0035), ESR (p=0.015), and low MPV (p=0.01) had significantly higher cumulative incidences of post-operative complications (Fig. 3).

There was a significant difference in the cumulative incidence of post-operative complications between the IST and non-IST groups (58.8% *vs.* 9.1%, p<0.001). The time to complication occurrence also differed significantly (23.21±20.33 *vs.* 10.19±12.53, p=0.016). IST group showed significantly higher complication-free survival rates (p<0.001), although there was no significant difference in long-term survival rates (p=0.2) (Fig. 4).

Comment

Behçet's disease

This study summarises the clinical characteristics and surgical outcomes of BD-related cardiovascular disease. Echocardiography can be used to evaluate cardiovascular involvement. The main cardiovascular manifestations

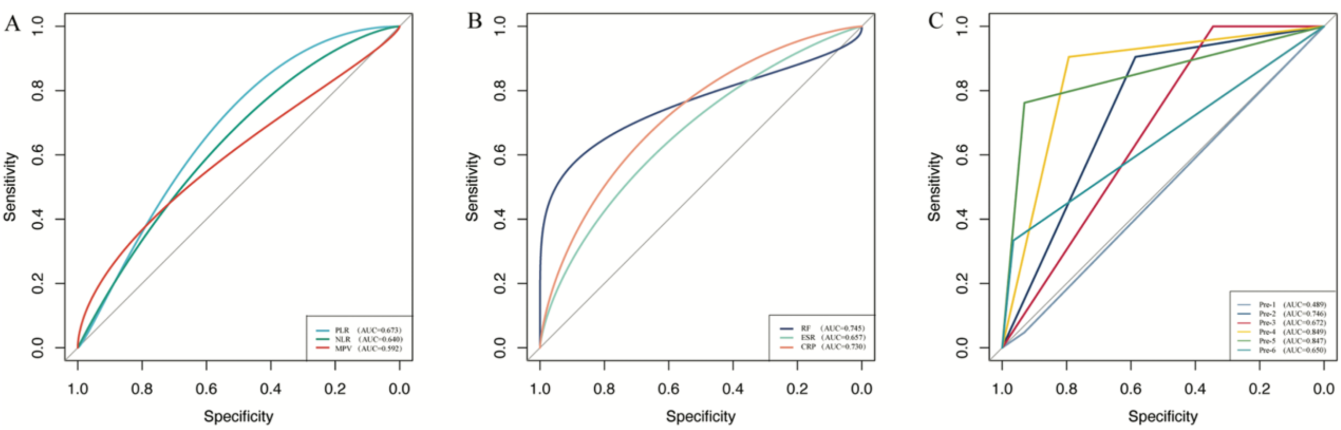

Fig. 2. Receiver operating characteristic curve of inflammatory indicators and predictive model.
A: ROC curve of novel inflammatory biomarkers; **B**: ROC curve of biochemical inflammatory biomarkers; **C**: ROC curve of predictive model.
ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; CRP: C-reactive protein; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; Pre-1:The clinical prediction model based on at least 1 positive biomarkers; Pre-2:The clinical prediction model based on at least 2 positive biomarkers; Pre-3:The clinical prediction model based on at least 3 positive biomarkers; Pre-4:The clinical prediction model based on at least 4 positive biomarkers; Pre-5:The clinical prediction model based on at least 5 positive biomarkers; Pre-6:The clinical prediction model based on at least 6 positive biomarkers.

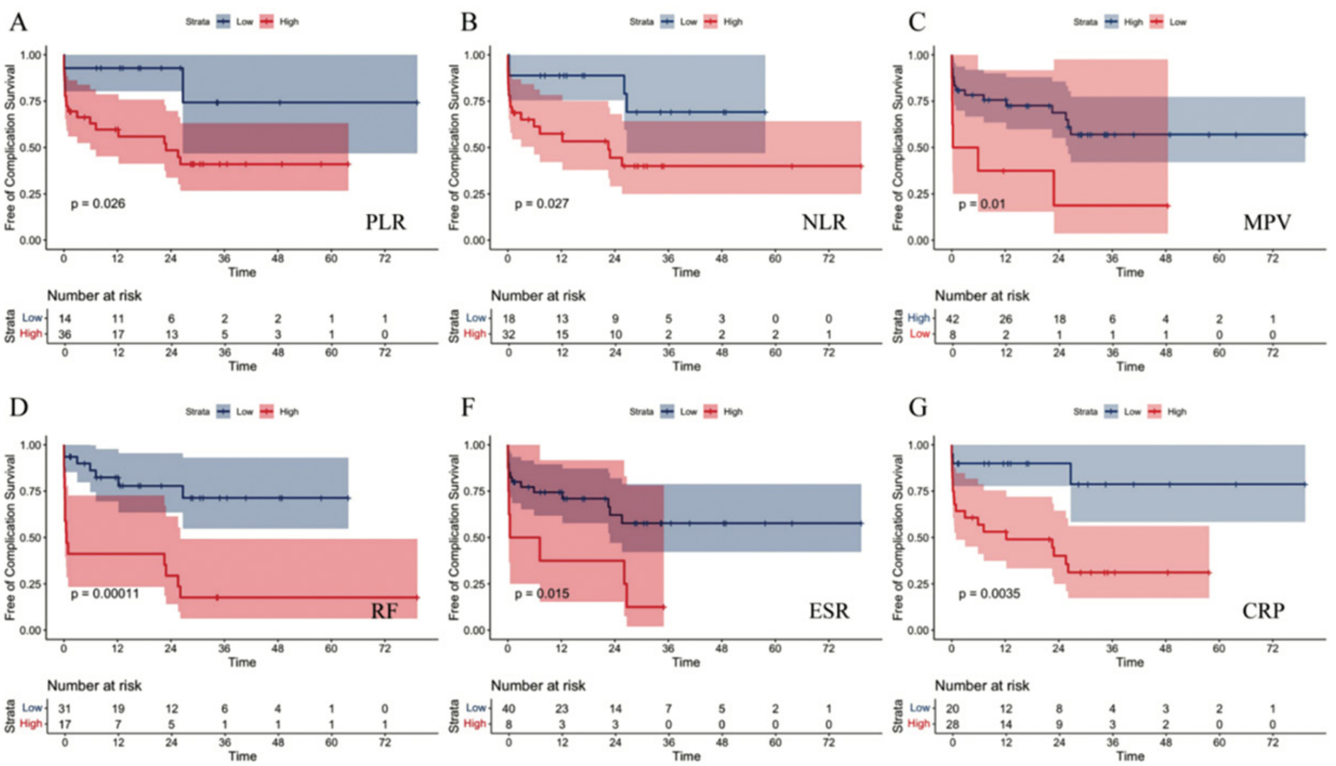

Fig. 3. Complication-free Kaplan-Meier curves for different inflammatory indicators grouped by cut-off points.
PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein.

of BD include severe aortic regurgitation, aortic valve prolapse, aneurysmal changes, and cardiac thrombosis. Aneurysmal prolapse may lead to left ventricular outflow tract obstruction, requiring heightened awareness of BD. Intracardiac thrombosis is an uncommon presentation of BD, typically occurring in the ventricles or right atrium. BD should be suspected in the absence of conventional high-risk factors for thromboembolism. Differentiation between BD and infective endocarditis (IE) requires attention to the characteristic feature of sterile aneurysmal changes. A study has highlighted the potential threat of asymptomatic cardiovascular involvement, underscoring the need for early detection through echocardiography or cardiac MRI (16).

Pre-operative immunosuppressive

Theoretically, pre-operative IST can help control the progression of vascu-

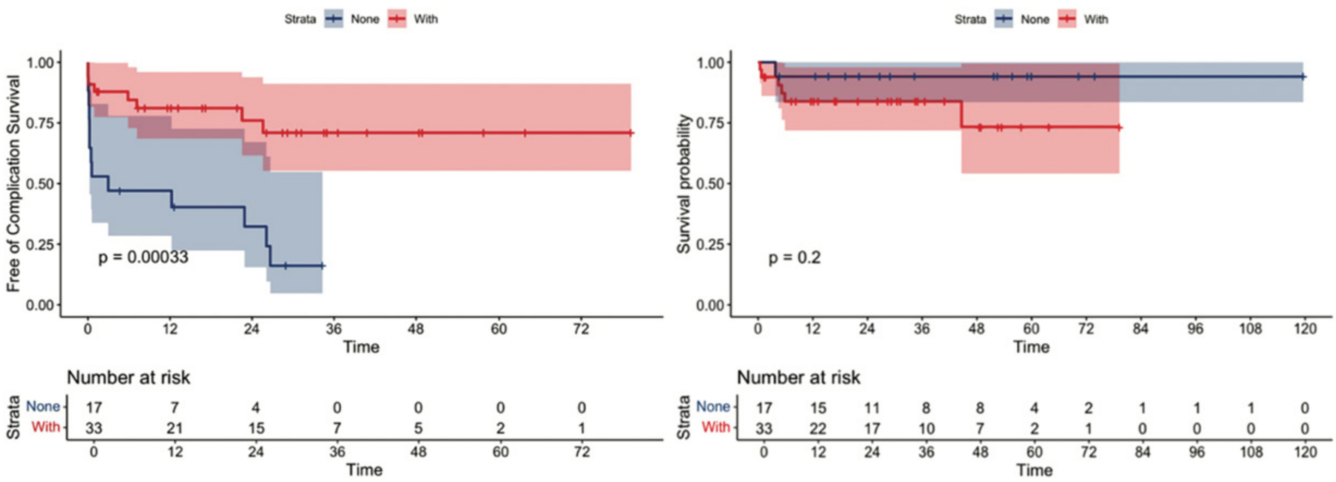

Fig. 4. Comparison of survival curves between groups with and without pre-operative immunosuppressive therapy.

litis and promote stabilisation of the periprosthetic tissues. In the IST group, we observed reduced endothelial damage, inflammatory cell infiltration, and fibrin deposition in the aortic wall. In this study, data showed that the IST group had lower inflammatory biomarkers, with a significant difference in RF (14.57±6.32 *vs.* 9.46±4.02, *p*=0.004), NLR (2.61±1.84 *vs.* 7.06±10.66, *p*=0.028), suggesting that the non-IST group pre-operatively was in an active inflammatory phase. Among patients receiving IST, those who developed complications had higher levels of these markers, with several showing significant differences (Suppl. Fig. S1). Therefore, regardless of immunosuppressive therapy status, we used these markers to assess pre-operative inflammatory activity and predict post-operative complications. Considering medication effects on neutrophils and lymphocytes, we analysed the neutrophils count and lymphocytes count between IST and Without IST group, the results showed that no significant differences.

Studies indicate that vascular inflammation is key in thrombosis in BD: pre-operative IST is associated with the complete resolution of intracardiac thrombosis (17). Research also confirms that PLR is an independent risk factor for lower limb venous thrombosis, with a PLR higher than 151 showing 77% sensitivity and 77.3% specificity for predicting thrombosis (18). In our study, one patient with right ventricular thrombosis who did not receive pre-operative IST had a PLR of 299. After thrombus removal surgery, the patient experienced recurrent right ventricular thrombosis two years later.

PVL is a major post-operative complication of BD. While IST has been shown to reduce PVL incidence significantly (6, 19), it was not confirmed in our study. Among 42 patients undergoing aortic valve replacement, four patients had PVL. A comparison of pre-operative markers between patients with and without PVL showed that RF was significantly higher in those with PVL (10.04±4.78 *vs.* 17.5±50, *p*=0.007), while MPV (10.77±1.22 *vs.* 9.5±1.24, *P*=0.099), PLR (142.43±130.23 *vs.* 113.34±19.56, *p*=0.95), and NLR (4.82±7.51 *vs.* 3.80±0.751, *p*=0.25) showed no significant differences. However, given this study's low incidence of PVL (8%) and short follow-up period, these biomarkers failed to demonstrate clear associations. Further large-scale studies are needed to explore these relationships.

Additionally, we found that NLR was higher in the IST group (7.06±10.6 *vs.* 2.61±1.84, *p*=0.028). Three patients had high NLR values (35.4, 34.57, 37.1). Excluding these outliers, no significant difference in NLR (3.94±3.60 *vs.* 2.77±1.74, *p*=0.319). One of them exhibited severe immune inflammation of the valves and large vessels post-operatively despite receiving IST, with persistently high inflammatory biomarkers. The other two patients had concomitant IE, and all three had poor post-operative outcomes despite pre-operative high-dose IST. These findings suggest that long-term high-dose IST and its association with subsequent IE may contribute to complications. This raises concerns regarding the perioperative use of IST in cardiovascular surgery patients. Pre-operative IST cannot be considered a "golden pardon" against complications, and surgical timing should be guided by close monitoring of inflammatory biomarkers to reduce post-operative complications. Furthermore, the side effects of IST warrant attention. In one case, a patient received long-term IST (including Tripterygium glycosides) but with higher pre-operative inflammatory markers (NLR: 36.58, PLR: 866.67) and concomitant IE. Long-term IST and dose adjustments increase infection and surgical risks, and the patient had a poor outcome. This highlights the need for rheumatology and immunology specialists to carefully evaluate IST regimens for such patients, balancing the potential risks of infection and surgical complications while managing active-phase inflammation.

Multivariate analysis

Research has proposed that high NLR is associated with endothelial dysfunction and can reflect the activity of BD (20). Previous studies have shown that an NLR cut-off of 1.455 predicts active BD with high sensitivity (93.8%) and specificity (71%), with an AUC of 0.844. These studies assessed disease activity using the Behçet's Disease Clinical Activity Form (BDCAF). Akkurt *et al.* proposed an NLR cut-off of

1.85, distinguishing active BD from inactive BD with 62.9% sensitivity and 61.6% specificity (21). Alan *et al*. suggested a cut-off of 2.5 for effectively distinguishing active BD (22). This study's NLR cut-off of 2.04 for perioperative cardiac patients predicted post-operative complications with 81% sensitivity and 48.3% specificity.

Additionally, PLR is a new biomarker of inflammation; a PLR cut-off of 144.05 showed a sensitivity of 62.5% and specificity of 57.1% (AUC=0.625) (22), while in our study, a PLR cut-off of 95.618 had a 90.5% sensitivity and 41.4% specificity.

In some studies, MPV, a novel inflammatory biomarker reflecting platelet activation and function, has been linked to BD involvement. Research has shown that MPV differs significantly between flare and stable BD, with lower MPV in the flare group (12). Although MPV did not show significant differences between groups in our study, it was identified as a protective factor in univariate analysis, with a high specificity of 93.1%.

Recent studies focus on single inflammatory biomarkers with low predictive efficacy, lacking comprehensive analysis of multiple markers. This study developed a clinical model combining inflammatory markers and pre-operative IST to predict post-operative complications. When ≥4 biomarkers were positive, the model achieved an AUC of 0.849, sensitivity of 90.5%, and specificity of 79.3%. We recommend assessing inflammatory markers after initiating IST in BD-related cardiovascular surgery candidates. If ≥4 biomarkers are positive, surgery should be delayed; otherwise, it can proceed, potentially reducing complications and improving outcomes.

Our study differs from previous research in the following ways: i) This study firstly uses inflammatory biomarkers in patients requiring cardiac surgery for cardiovascular involvement in BD. Individual variations in cardiovascular manifestations may reduce biomarker sensitivity; ii) Previous studies highlighted the necessity of pre-operative IST but without further research. Our study further evaluates the effectiveness of pre-operative IST and builds a clinical model, comprehensively assessing pre-operative inflammatory status and surgical timing; iii) We used post-operative complications as the outcome measure to assess whether these biomarkers can evaluate the inflammatory state and guide appropriate surgical timing, thereby reducing post-operative complications.

The main study limitation is that the results cannot fully confirm the predictive performance, due to the small sample size and retrospective nature of the study. Additionally, some patients receiving IST had short follow-up durations, during which complications may not have been observed. More extensive prospective studies are needed to provide convincing findings.

References

1. LAKHANPAL S, TANI K, LIE JT, KATOH K, ISHIGATSUBO Y, OHOKUBO T: Pathologic features of Behçet's syndrome: a review of Japanese autopsy registry data. *Hum Pathol* 1985; 16(8): 790-95. https://doi.org/10.1016/s0046-8177(85)80250-1
2. MARZBAN M, MANDEGAR MH, KARIMI A *et al*.: Cardiac and great vessel involvement in 'Behçet's disease'. *J Card Surg* 2008; 23(6): 765-68. https://doi.org/10.1111/j.1540-8191.2008.00607.x
3. JEONG DS, KIM KH, KIM JS, AHN H: Long-term experience of surgical treatment for aortic regurgitation attributable to Behçet's disease. *Ann Thorac Surg* 2009; 87(6): 1775-82. https://doi.org/10.1016/j.athoracsur.2009.03.008
4. SONG JK, KIM MJ, KIM DH *et al*.: Factors determining outcomes of aortic valve surgery in patients with aortic regurgitation due to Behçet's disease: impact of preoperative echocardiographic features. *J Am Soc Echocardiogr* 2011; 24(9): 995-1003. https://doi.org/10.1016/j.echo.2011.06.006
5. AHN JK, KIM H, LEE J *et al*.: Treatment outcomes in patients with non-infectious aortic valvulitis undergoing aortic valve replacement: implication for the treatment of aortic valve involvement in Behçet's disease. *Rheumatol Int* 2009; 29(11): 1391-93. https://doi.org/10.1007/s00296-009-0862-2
6. CHOI HM, KIM HK, PARK SJ *et al*.: Predictors of paravalvular aortic regurgitation after surgery for Behçet's disease-related severe aortic regurgitation. *Orphanet J Rare Dis* 2019; 14(1): 132. https://doi.org/10.1186/s13023-019-1083-8
7. BHAT T, TELI S, RIJAL J *et al*.: Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther* 2013; 11(1): 55-59. https://doi.org/10.1586/erc.12.159
8. LEE JS, KIM NY, NA SH, YOUN YH, SHIN CS: Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine* (Baltimore) 2018; 97(26): e11138. https://doi.org/10.1097/md.0000000000011138
9. YUKSEL M, YILDIZ A, OYLUMLU M *et al*.: Novel markers of endothelial dysfunction and inflammation in Behçet's disease patients with ocular involvement: epicardial fat thickness, carotid intima media thickness, serum ADMA level, and neutrophil-to-lymphocyte ratio. *Clin Rheumatol* 2016; 35(3): 701-8. https://doi.org/10.1007/s10067-015-2907-0
10. OZTURK C, BALTA S, BALTA I *et al*.: Neutrophil-lymphocyte ratio and carotid-intima media thickness in patients with Behçet disease without cardiovascular involvement. *Angiology* 2015; 66(3): 291-96. https://doi.org/10.1177/0003319714527638
11. ALAN S, TUNA S, TÜRKOĞLU EB: The relation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume with the presence and severity of Behçet's syndrome. *Kaohsiung J Med Sci* 2015; 31(12): 626-31. https://doi.org/10.1016/j.kjms.2015.10.010
12. RYU HJ, SEO MR, CHOI HJ, KO KP, PARK PW, BAEK HJ: Mean platelet volume as a marker for differentiating disease flare from infection in Behçet's disease. *Int J Rheum Dis* 2018; 21(8): 1640-45. https://doi.org/10.1111/1756-185x.13008
13. LEE YH, SONG GG: Neutrophil-to-lymphocyte ratio, mean platelet volume and platelet-to-lymphocyte ratio in Behçet's disease and their correlation with disease activity: a meta-analysis. *Int J Rheum Dis* 2018; 21(12): 2180-87. https://doi.org/10.1111/1756-185X.13404
14. INTERNATIONAL TEAM FOR THE REVISION OF THE INTERNATIONAL CRITERIA FOR BEHÇET'S DISEASE (ITR-ICBD): The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; 28(3): 338-47. https://doi.org/10.1111/jdv.12107
15. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335(8697): 1078-80.
16. PU L, LI R, XIE J *et al*.: Characteristic echocardiographic manifestations of Behçet's disease. *Ultrasound Med Biol* 2018; 44(4): 825-30. https://doi.org/10.1016/j.ultrasmedbio.2017.12.010
17. GERI G, WECHSLER B, THI HUONG DL *et al*.: Spectrum of cardiac lesions in Behçet disease: a series of 52 patients and review of the literature. *Medicine* (Baltimore) 2012; 91(1): 25-34. https://doi.org/10.1097/MD.0b013e3182428f49
18. ERDEN F, KARAGOZ H, AVCI A *et al*.: Which one is best? platelet/lymphocyte ratio, neutrophil/lymphocyte ratio or both in determining deep venous thrombosis in Behçet's disease? *Biomedical Res* (India) 2017; 28: 5304-9.
19. GUO X, TIAN Z, LIU Y, LI M, ZENG X, FANG Q: Preoperative immunosuppressive therapy reduces paravalvular leakage after aortic valve surgery in patients with aortic regur-

gitation attributable to Behçet's disease. *Clin Exp Rheumatol* 2016; 34 (Suppl. 102): S26-33.
20. BALTA S, OZTURK C, BALTA I *et al.*: The neutrophil-lymphocyte ratio and inflammation. *Angiology* 2016; 67(3): 298-99. https://doi.org/10.1177/0003319715615252
21. BALKARLI A, KUCUK A, BABUR H, ERBASAN F: Neutrophil/lymphocyte ratio and mean platelet volume in Behçet's disease. *Eur Rev Med Pharmacol Sci* 2016; 20(14): 3045-50.
22. HAMMAD M, SHEHATA OZ, ABDEL-LATIF SM, EL-DIN AMM: Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use? *Clin Rheumatol* 2018; 37(10): 2811-17. https://doi.org/10.1007/s10067-018-4194-z