New insight into therapeutic strategy and prognostic predictors in patients with cardiac Behçet's Syndrome: from the Shanghai Behçet's Syndrome database

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Research Article

Keywords: Behçet's Syndrome, Bentall procedure, JAK inhibitor, Biological agent, Prognostic predictors

Posted Date: April 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1558146/v1

Abstract

Background

Cardiac Behçet's syndrome (cardiac BS) is rare but lethal. And the influencing factors of prognoses in cardiac BS are not clear. This study was conducted to summarize the features of cardiac BS and find the predictors of unfavourable prognoses for cardiac BS patients.

Methods

Sixty-six cardiac BS patients were included from 1467 BS patients in the Shanghai Behçet's syndrome database. The median follow-up duration was 4.0 (2.0–7.0) years. The unfavourable prognosis was defined as a compound event containing all-cause death and rehospitalization related to worsened cardiac lesions or postoperative complications. Logistic regression analyses were performed to evaluate the predictors of unfavourable prognoses.

Results

In this study, the mortality rate of cardiac BS patients was 10.61% (7/66), and 22 (33.33%) patients experienced two or more surgeries. Ninety-six cases were collected from 66 cardiac BS patients. The effective rates of postoperative biological agents and Janus kinases (JAK) inhibitors in cardiac BS patients were 88.89% (16/18) and 81.25% (13/16) respectively. Former smoking, valve replacement or repairment and poor compliance were found to be the independent risk factors of unfavourable prognoses; preoperative immunosuppressive therapies and postoperative immunosuppressive therapies were independent protective factors for unfavourable prognoses in total cardiac BS. In 65 cases of cardiac BS after aortic valve surgeries, former smoking was an independent risk factor for unfavourable prognoses. Bentall procedure, postoperative traditional DMARDs, postoperative JAK inhibitors or biological agents were independent protective factors for unfavourable prognoses in cardiac BS patients after aortic valve surgeries.

Conclusion

Both preoperative immunosuppressive therapies and postoperative immunosuppressive therapies are necessary for cardiac BS patients. Bentall procedure is recommended to be performed in BS patients with severe AR. Besides biological agents, JAK inhibitors can be used in cardiac BS patients after aortic valve surgeries for promoting favourable outcomes.

Introduction

Behçet's syndrome (BS) is a rare chronic variable-vessel vasculitis of unknown aetiology, characterized by recurrent oral ulcers, genital ulcers, skin lesions and multisystemic involvements [1]. Cardiac BS was diagnosed when BS patients were detected with valvular regurgitation, especially aortic regurgitation (AR), intracardiac thrombi, or coronary artery disease [2]. Cardiac BS is extremely uncommon [3], which accounts for only 5.1% of the total Chinese BS patients in the previous research of our centre [2]. However, the cardiac lesion is the leading cause of BS mortality and the treatment is challenging [4]. Because of the frequently occurring postoperative complications like postoperative paravalvular leakage (PVL) and pseudoaneurysm, many cardiac BS patients ended with reoperation or even death.

Limited studies reported the influencing factors of prognoses in cardiac BS. And the sample sizes of those studies were quite small, ranging from 20 to 41 patients [4–6]. Postoperative immunosuppressive therapy, perioperative management with biologics and concomitant aortic root replacement seemed to be helpful to reduce the occurrence of serious postoperative complications [4–6]. To establish a more suitable therapy and to reduce rates of postoperative complications and mortality, we included 66 patients and conducted this case-control study to summarize the features of cardiac BS and find the predictors of unfavourable prognoses in cardiac BS.

Patients And Methods

Patients

Cardiac BS patients were identified from the continually updated Shanghai Behçet's syndrome database [7, 8], and were followed up in the Department of Rheumatology and Immunology of Huadong Hospital from October 2012 to January 2022. Patients were diagnosed with definite cardiac BS when they fulfilled the 2014 International Criteria for Behçet's Disease (ICBD) [9] and were detected valvular regurgitation, intracardiac thrombi, or coronary artery disease by echocardiography or coronary angiography and/or CT as well [2]. Patients with oral ulcers, not fulfilling the 2014 ICBD criteria, but accompanied by cardiac lesions, were diagnosed with suspected cardiac BS by consensus determination of rheumatologists, pathologists, and cardiac surgeons. Exclusion criteria included: (1) valvular regurgitation, intracardiac thrombi, or coronary artery disease caused by other diseases, such as infectious endocarditis, rheumatic fever, Marfan syndrome, syphilis and congenital heart disease, (2) patients with malignancy, chronic infectious diseases, or other rheumatic diseases. Poor compliance of cardiac BS patients was defined as who did not follow the directions of cardiac surgeons and rheumatologists.

Drug Administration

Preoperative immunosuppressive therapy and postoperative immunosuppressive therapy included corticosteroids and immunosuppressants. The immunosuppressants consisted of traditional disease-modifying antirheumatic drugs (DMARDs), biological agents and Janus kinases (JAK) inhibitors. DMARDs were most frequently cyclosporin A (3-6 mg/kg/day), thalidomide (0.5-1.5 mg/kg/day) and colchicine 1mg/day. JAK inhibitors contained tofacitinib (5 mg twice/day) and baricitinib (2 mg/day).

The biological agents used in cardiac BS patients included infliximab, adalimumab, tocilizumab, golimumab and anti-TNF fusion protein. Patients received infliximab (3-5 mg/kg) intravenously at 0, 2, and 6 weeks, and every 4-8 weeks thereafter. Adalimumab was administrated subcutaneously at 40 mg every 2 weeks. Tocilizumab (8 mg/kg) was administrated intravenously every 4 weeks. Golimumab was injected subcutaneously at 50 mg/ 4 weeks. And anti-TNF fusion protein was used at a dose of 25 mg twice a week subcutaneously. The frequency and dosage of JAK inhibitors and biological agents were adjusted according to the clinical conditions of cardiac BS patients. The dosage of corticosteroids at the beginning was 0.5-1 mg/kg/day of prednisolone for 1-2 weeks, and was gradually decreased to stop or maintained at a low dosage (5-10 mg/day) when stabilization or clinical improvement was observed.

Outcome assessment and data collection

The outcome assessment of unfavourable prognoses was defined as a compound event containing all-cause death and rehospitalization. The rehospitalization was related to worsened cardiac lesions or postoperative complications, like postoperative paravalvular leakage (PVL) and pseudoaneurysm. On the opposite, the patient with a favourable prognosis was defined as a patient in stable condition who did not undergo rehospitalization because of cardiac lesions or surgery.

The following information was collected at baseline: gender, age, age at cardiac lesions onset, duration of BS, duration of cardiac lesions, body mass index (BMI), diagnosis, clinical manifestations of BS (oral ulcer, genital ulcer, uveitis, erythema nodosum, pseudofolliculitis pathergy reaction, intestinal, vascular, hematologic, joint, cardiac, neurological and blood involvement). The preoperative, postoperative and surgery information of each surgery was collected: duration of BS at surgery, duration of cardiac lesions at surgery, age at surgery, smoking and drinking history, concomitant basic diseases (hypertension, diabetes, renal insufficiency, and hyperlipidemia), cardiac symptoms, New York Heart Association functional status, clinical manifestations of BS, scores of Behçet's Disease Current Activity Form (BDCAF) [10, 11], preoperative laboratory indexes [white blood cells (WBC), haemoglobin (Hb), platelets(PLT), neutrophil-to-lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], preoperative electrocardiogram, preoperative imageological examinations (echocardiography, CT angiography), dates of surgeries, surgical procedures, preoperative and postoperative immunosuppressive therapies (oral steroid, DMARDs, JAK inhibitor, and biological agent), and postoperative complications. In addition, the outcomes of cardiac BS patients were recorded.

Statistical analysis

The quantitative data was expressed as median [25th-75th interquartile range (IQR)], and qualitative data was recorded as number (%). Quantitative data analysis was performed by Student's t-test and Mann-Whitney U test. Chi-square test and Fisher's exact test were used for qualitative data analysis. Only the significant variables ($P < 0.05$) in univariable binary logistic regression were included in the multivariable models. Multivariate binary logistic regression was used by the stepwise backward method to predict the predictors of unfavourable prognoses in the 66 cardiac BS patients and in patients who underwent

surgeries for severe AR respectively. The performance of predicting models was evaluated by the area under the receiver operating characteristic curve (ROC AUC). Statistical analyses were conducted using the Statistical Package for Social Sciences (IBM SPSS) version 22 (Chicago, IL, USA) and GraphPad Prism version 8.0.0 (San Diego, California USA). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics and outcomes of cardiac BS patients

There were 66 cardiac BS patients [aged 43.0 (31.5-48.8) years, 84.85% male] selected from 1950 patients in the Shanghai Behçet's syndrome database. After deduplication, 1467 BS patients remained in the database. The proportion of cardiac BS in total BS was 4.50% (66/1467) from Shanghai Behçet's syndrome database. The median follow-up time was 4.0 (2.0-7.0) years, ranging from 1.0 to 9.5 years. Baseline characteristics and outcomes of the 66 cardiac patients are summarized in Table 1. The number of male cardiac BS patients was 5.6 times (56/10) the number of female patients. In the 66 patients, 47 patients were definite cardiac BS patients, and 19 patients were suspected cardiac BS patients.

In the follow-up duration, 54 (81.82%) patients were in stable condition. Death occurred in 7 (10.61%) patients, among whom, cardiac death occurred in 5 (7.58%) patients, 1 (1.52%) patient died of severe pneumonia, 1 patient died of ruptured aneurysm of ascending aorta. Five (7.58%) patients underwent rehospitalization owing to worsened cardiac lesions or postoperative complications (heart failure in non-operated patients with severe AR: 4 patients, postoperative paravalvular leakage: 1 patient) (Table 1, Figure 1a).

Twenty-two (33.33%) patients experienced two or more surgeries, of whom 2 patients underwent 4 surgeries and 4 patients had 3 surgeries. Notably, the outcomes of each surgery were different, even in the same patient. To find the influencing factors of the prognoses of cardiac BS patients, we observed the outcome of every surgery in each patient. And the 66 patients were collected as 96 cases. In the 96 cases, 35 cases were rehospitalized due to worsened cardiac lesions (4 cases) or postoperative complications (31 cases) (Table 1, Figure 1b).

Preoperative clinical characteristics of the 96 cases of cardiac BS patients

In the 96 cases, favourable prognoses were observed in 54 cases, and 42 cases ended with poor prognosis. No difference in prognoses was found in definite cardiac BS patients and suspected cardiac BS patients. The smoking status was different in patients with favourable or unfavourable prognoses. The case numbers of current and former smokers with unfavourable prognoses were significantly larger than cases with favourable prognoses ($P = 0.007$ and $P = 0.004$, Table 2). Compared to cases with unfavourable prognoses, more cases with palpitation before surgery achieved favourable prognoses ($P = 0.043$, Table 2). And basic diseases, including hypertension, diabetes, renal insufficiency and hyperlipidemia, did not influence the outcomes of cardiac BS patients in the current study (all $P > 0.05$,

Table 2). NO statistical difference was found in the levels of WBC, Hb, PLT, NLR and ESR between groups with opposite outcomes (Table 3). The CRP levels in cases with unfavourable prognoses were significantly higher than that in cases with favourable prognoses (P = 0.007, Table 3).

Surgical procedures

The surgical procedures significantly influenced the prognoses of cardiac BS patients (P = 0.005, Table 4). The outcomes of cases undergoing the Bentall procedure were significantly better than those who did not (P = 0.003). Cases that performed cardiac valve replacement or repairment operations suffered worse outcomes than cases treated by other surgical procedures (P = 0.000). Besides, it showed that the operation frequency did not influence the outcomes of cardiac BS patients (P = 0.655, Table 4).

Immunosuppressive therapies

Both preoperative and postoperative immunosuppressive therapies could promote favourable outcomes for cardiac BS patients (both P = 0.000, Table 5). And the treatment of preoperative and postoperative JAK inhibitor or biological agent seemed to be conducive to a good outcome (P = 0.044 and P = 0.000, Table 5). Regularly used postoperative biologics included: tocilizumab (n=1) and golimumab (n=1) ending with unfavourable prognoses, infliximab (n=1), adalimumab (n=3), etanercept (n=2) and other anti-TNF fusion protein (n=10) achieving good outcomes. The median observation time of postoperative biologics was 24.0 (15.5-38.0) months. The effective rate of postoperative biological agents was 88.89% (16/18, Figure 2a). Biological agents failed in two patients. One patient redid operation after using tocilizumab for the sake of postoperative PVL after aortic valve replacement (4 months later). The other patient using golimumab underwent reoperation due to postoperative cardiac vascular pseudoaneurysm after aortic arch aneurysm embolization (9 months later). No adverse reaction was observed in cardiac BS patients treated by biologics.

The effective rate of postoperative JAK inhibitor in cardiac BS patients was 81.25% (13/16, Figure 2b). JAK inhibitors included tofacitinib (11 patients with good outcome, 3 patients with poor outcome) and baricitinib (2 patients with good outcome). The median observation time was 16.5 (12.5-22.5) months. No patient underwent secondary surgery. But, after using tofacitinib for one year, one patient died from severe pneumonia 2 months after the Bentall procedure and one patient died of sudden cardiac death 1 year after the Cabrol procedure. Another patient with poor outcome after postoperative tofacitinib treatment occurred pseudoaneurysm 8 months after the Bentall procedure.

Predictors of unfavourable prognoses in 96 cases of cardiac BS

By multivariate logistic regression analysis, former smoking (OR: 8.17, 95% CI: 1.84-36.32, P = 0.006), valve replacement or repairment operation (OR: 13.49, 95% CI: 2.64-68.97, P = 0.002) and poor compliance (OR: 7.50, 95% CI: 1.42-39.62, P = 0.002) were found the independent risk factors of unfavourable prognoses in cardiac BS. Preoperative immunosuppressive therapies (OR: 0.23, 95% CI: 0.06-0.90, P = 0.035) and postoperative immunosuppressive therapies (OR: 0.22, 95% CI: 0.05-0.95, P =

0.043) were independent protective factors for unfavourable prognoses in cardiac BS (Table 6). The AUC of the predicting model of unfavourable prognoses in cardiac BS was 0.92 (95% CI: 0.86-0.98, P = 0.000), indicating a good accuracy of the model.

Predictors of unfavourable prognoses in 65 cardiac BS cases who underwent surgery for severe AR.

Former smoking (OR: 12.49, 95% CI: 1.04-149.94, *P* = 0.046) was an independent risk factor of unfavourable prognoses in cardiac BS patients undergoing surgeries for severe AR. Bentall procedure (OR: 0.07, 95% CI: 0.01-0.78, *P* = 0.031), postoperative DMARDs (OR: 0.02, 95% CI: 0.00-0.26, *P* = 0.002) and postoperative JAK inhibitor or biological agent (OR: 0.16, 95% CI: 0.03-0.94, *P* = 0.043) were independent protective factors for unfavourable prognoses in BS patients after aortic valve surgeries (Table 7). The predicting model of unfavourable prognoses in cardiac BS patients undergoing surgeries for severe AR had a satisfactory accuracy with AUC equalling to 0.93 (95% CI: 0.88-0.99, P = 0.000).

Discussion

This case-control study on cardiac BS aimed to find out predictors of unfavourable prognoses, including all-cause death and rehospitalization caused by cardiac lesions or postoperative complications.

In the current study, former smoking was found to be a risk factor for unfavourable prognoses in both total cardiac BS and cardiac BS patients undergoing surgeries for AR. It is not clear about the relationship between smoking and BS now. A previous study in South Korea showed a decreased incidence of BS in current smokers compared with never smokers [12]. While a study in Iran showed that disease activity in former smokers was significantly higher than in never smokers [13]. Smoking is one of the most common addictive habits which result in inflammatory reactions [12]. The negative effect of smoking on cardiovascular outcomes is well established. Five-year follow-up results of 18 randomized trials demonstrated that smoking was an important predictor of adverse outcomes after percutaneous coronary intervention (PCI) with stent implantation [14]. In heart transplant, donor smoking was related to the increased rate of mortality and graft failure [15]. Therefore, smoking might promote unfavourable prognoses in cardiac BS by increasing inflammatory reactions.

It showed in this study that valve replacement or repairment was an independent risk factor of unfavourable prognoses in total cardiac BS, and Bentall procedure was an independent protective factor for unfavourable prognoses in BS patients undergoing aortic valve surgeries. Choi et al [4] showed that concomitant aortic root replacement was an independent protective factor of PVL. PVL is a major indication for reoperation after aortic valve surgery, which might be caused by improper suture skills, prosthetic valve endocarditis, and non-specific vasculitis [16]. Damage to the unhealthy aorta can cause exaggerated inflammatory response in cardiac BD patients. So, it may cause dehiscence and PVL when a mechanical or bioprosthetic valve was sutured to the inflamed aortic root [4]. Bentall procedure is a type of open-heart surgery by using a composite graft to replace the aortic valve, aortic root, and ascending aorta, which can dramatically prevent PVL and decrease the reoperation rate in cardiac BS patients [4, 16].

In our previous study, poor compliance (OR 11.730 [95% CI 2.341–58.781]) was an independent risk factor for adverse outcomes in intestinal BS patients [7]. And in the current study, poor compliance was found the independent risk factor of unfavourable prognoses in cardiac BS. The poor compliance in cardiac BS patients was usually related to irregularly taking immunosuppressive medications, which might be related to side effects of medicines, economic pressure and long disease course.

The clinical symptoms of BS patients with AR were usually too few to fulfil the 2014 ICBD criteria [4]. So, some patients were performed operations without being diagnosed with BS or treated by immunosuppressants. Guo et al [17] showed that preoperative immunosuppressive therapy could reduce postoperative PVL and improve the outcomes in BS patients with severe AR. Some researchers had different conclusions: postoperative, but not preoperative immunosuppressive therapies were helpful to reduce the occurrence of PVL [4, 5]. While previous research illustrated that preoperative activated inflammatory status was related to mortality in patients undergoing cardiac surgeries [18]. In this study, preoperative immunosuppressive therapies and postoperative immunosuppressive therapies were both independent protective factors of unfavourable prognoses in cardiac BS (Table 6).

Postoperative DMARDs were found to be a helpful concomitant therapy in BS patients after aortic valve surgeries (Table 7). Saadoun et al [19] found that immunosuppressants, mainly including intravenous cyclophosphamide continued with azathioprine, were associated with complete remission in BD patients with arterial involvement. And 2018 EULAR recommendations for BS summarized that medical treatment is necessary along with surgery or stenting for decreasing the risk of postoperative complications and recurrences [20]. Our result is in correspondence with the previous studies.

Postoperative JAK inhibitor or biological agent was an independent protective factor for unfavourable prognoses in BS patients who underwent AR surgeries (Table 7). The effective rate of postoperative biologics in cardiac BS patients was 88.89% (16/18). Two patients underwent reoperation owing to postoperative PVL after aortic valve replacement and postoperative pseudoaneurysm after aortic arch aneurysm embolization, respectively. No adverse reaction was observed in cardiac BS patients treated by biologics. Kawakubo et al [21] reported a case with severe acute AR due to BS who was successfully treated by the concomitant use of immunomodulatory agents with infliximab for perioperative use. Sun et al [6] retrospectively analyzed 20 BS patients with severe AR treated with biologics, and found that biologics significantly hindered postoperative PVL and had a sparing effect on glucocorticoid and immunosuppressants. The current study also showed good efficacy and safety of biologics in cardiac BS, mainly TNF inhibitors.

In the current study, postoperative JAK inhibitors were effective in 81.25% (13/16) of cardiac BS patients. Our previous study showed that tofacitinib contributed to a rapid and sustained improvement in vision and ocular inflammation during a follow-up time ranging between 24 and 38 months [22]. Another retrospective study showed that tofacitinib decreased overall disease activity and induced remission of cardiac/vascular and articular involvement in BS patients [23]. However, some studies reported increased

thromboembolism with tofacitinib, especially in patients with tofacitinib 10 mg twice daily [1, 24]. As a result, no patient was observed thrombosis with tofacitinib 5 mg twice daily in this study. But, one patient died from severe pneumonia 2 months after Bentall procedure with one-year tofacitinib therapy. The previous study on inflammatory bowel diseases patients treated with tofacitinib showed that 6% (17/305) of the patients had an infection-related hospitalization, and the most frequent infections were respiratory tract and urinary infections [25]. And there was no significant difference in the rate of infection or infection-related hospitalizations between anti-TNF and tofacitinib [25]. In a study on pulmonary adverse events of JAK inhibitors in rheumatoid arthritis (RA) patients, the rates of suffering from pneumonia after taking tofacitinib were similar to that of other drugs, like methotrexate and adalimumab [26].

The above studies indicated that JAK inhibitors may have a satisfying treatment effect on arterial vascular involvement in BS [1]. Although one patient treated with tofacitinib died of severe pneumonia in the current study, the previous research showed the rate of infection in autoimmune disease was similar between TNF inhibitors and JAK inhibitors [25, 26]. Moreover, TNF inhibitors may cause heart failure or arrhythmia, while no side effect related to heart was reported in patients treated with tofacitinib or baricitinib. Therefore, JAK inhibitors may have the potential to be a more preferred choice for cardiac BS patients, after proven effective by further larger-scale investigations.

The main limitations of the current study stem from the retrospective nature. Although multiple analyses were used to find out the predictors of the unfavourable outcomes of cardiac BS, we could not elucidate other potential unmeasured confounders. And the study was single-centre, which may lead to admission bias. While our patients coming from all over China may minimize such bias. Future multicenter and prospective studies are needed to verify the conclusions of the study.

Conclusions

Both preoperative immunosuppressive therapies and postoperative immunosuppressive therapies are needed in cardiac BS patients. Bentall procedure is suggested to be performed in BS patients with severe AR. Postoperative JAK inhibitor or biological agent is an independent protective factor of poor prognosis in BS patients who had undergone AR surgeries. Besides biological agents, can be used to treat cardiac BS as well.

Declarations

Acknowledgements

We would like to thank Xinxin Xu from the Clinical Research Center of Geriatrics, Huadong hospital for the instructive advice in statistical analysis.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Huadong Hospital affiliated to Fudan University (reference numbers: 2016K044 and 2018K031) and complied with the Declaration of Helsinki. No need for written informed consent was required, owing to the anonymized data and the retrospective nature of this study.

Authors' contributions

Hua-fang Bao performed data acquisition and drafted the manuscript. Jian-long Guan designed the study. Cheng-cheng Hou and Jian-fei Cai performed the statistical analysis. Kai-tao Jian, Dan Luo, Jing-fen Ye and Chun-hui She collected data. All authors read and approved the final manuscript.

Funding

This work is supported by the National Natural Science Foundation of China [81871276].

Data availability statement

Please contact the corresponding author for data requests.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Tables

Table 1. Baseline characteristics and outcomes of the cardiac BS patients

	Total (n= 66)
Baseline	
Gender (male), n (%)	56 (84.85)
Age (years)	43.0 (31.5-48.8)
Age at cardiac lesions onset (years)	36.0 (29.0-46.0)
Duration of BS (years)	10.0 (5.0-18.0)
Duration of cardiac lesions (years)	1.0 (0.5-4.0)
BMI	21.48 (20.26-24.70)
Fulfilment of 2014 ICBD criteria, n (%)	
Definite	47 (71.21)
Suspected	19 (28.79)
Oral ulcers, n (%)	66 (100.00)
Genital ulcers, n (%)	40 (60.61)
Uveitis, n (%)	4 (6.06)
Erythema nodosum, n (%)	25 (37.88)
Pseudofolliculitis, n (%)	23 (34.85)
Intestinal ulcers, n (%)	3 (4.55)
Vascular involvement, n (%)	17 (25.76)
Hematologic involvement, n (%)	0 (0.00)
Nervous system involvement, n (%)	1 (1.52)
Joint involvement, n (%)	5 (7.58)
Positive pathergy reaction, n (%)	4 (6.06)
Outcomes	
Stabilization, n (%)	54 (81.82)
Death, n (%)	7 (10.61)
Cardiac death, n (%)	5 (7.58)
Caused by severe pneumonia, n (%)	1 (1.52)
Caused by ruptured aneurysm of ascending aorta, n (%)	1 (1.52)
Rehospitalization, n (%)	5 (7.58)

Non-operated patients, n (%)	4 (6.06)
Postoperative paravalvular leakage, n (%)	1 (1.52)
≥ 2 surgeries, n (%)	22 (33.33)
Rehospitalization, cases	35
Postoperative PVL, cases	26
Postoperative arterial anastomosis fistula, cases	2
Postoperative cardiac vascular pseudoaneurysm, cases	3
Non-operated severe AR, cases	4

BMI, body mass index.

Table 2. Preoperative clinical characteristics of the 96 cases in cardiac BS patients

	Favourable prognoses n=54	Unfavourable prognoses n=42	*P*
Gender (male), n (%)	46 (85.19)	34 (80.95)	0.581
Diagnosis, n (%)			0.284
Definite BS	39 (72.22)	26 (61.90)	/
Suspected BS	15 (27.78)	16 (38.10)	/
Duration of BS at surgery (years)	9.0 (4.8-14.5)	7.0 (3.0-12.3)	0.462
Duration of cardiac lesions at surgery (years)	0.5 (0.0-1.0)	0.5 (0.2-3.0)	0.117
Age at surgery (years)	40.0 (31.8-45.5)	39.0 (30.5-47.3)	0.788
Current smoker, n (%)	5 (9.26)	13 (30.95)	0.007*
Former smoker, n (%)	15 (27.78)	24 (57.14)	0.004*
Current drinker, n (%)	4 (7.41)	8 (19.05)	0.087
Former drinker, n (%)	14 (25.93)	15 (35.71)	0.300
Exertional dyspnea, n (%)	36 (66.67)	33 (78.57)	0.198
Orthopnea, n (%)	14 (25.93)	12 (28.57)	0.772
Chest tightness, n (%)	34 (62.96)	31 (73.81)	0.260
Chest pain, n (%)	14 (25.93)	10 (23.81)	0.812
Palpitation, n (%)	10 (18.52)	2 (4.76)	0.043*
Amaurosis, n (%)	3 (5.56)	5 (11.90)	0.457
Dizziness, n (%)	7 (12.96)	2 (4.76)	0.310
Cough, n (%)	5 (9.26)	2 (4.76)	0.656
Fever, n (%)	3 (5.56)	3 (7.14)	0.915
Hypertension, n (%)	4 (7.41)	2 (4.76)	0.915
Diabetes, n (%)	0 (0.00)	0 (0.00)	1.000
Renal insufficiency, n (%)	0 (0.00)	1 (2.38)	0.438
Hyperlipemia, n (%)	0 (0.00)	1 (2.38)	0.438
New York Heart Association functional status, n (%)			0.420
I	8 (14.81)	2 (4.76)	/

II	17 (31.48)	13 (30.95)	/
III	14 (25.93)	14 (33.33)	/
IV	15 (27.78)	13 (30.95)	/
Oral ulcers, n (%)	46 (85.19)	39 (92.86)	0.397
Genital ulcers, n (%)	27 (50.00)	21 (50.00)	1.000
Uveitis, n (%)	3 (5.56)	1 (2.38)	0.797
Erythema nodosum, n (%)	18 (33.33)	8 (19.05)	0.118
Pseudofolliculitis, n (%)	16 (29.63)	18 (42.86)	0.179
Intestinal ulcers, n (%)	3 (5.56)	0 (0.00)	0.337
Vascular involvement, n (%)	15 (27.78)	9 (21.43)	0.476
Hematologic involvement, n (%)	0 (0.00)	0 (0.00)	1.000
Nervous system involvement, n (%)	1 (1.85)	0 (0.00)	1.000
Joint involvement, n (%)	5 (9.26)	2 (4.76)	0.656
Positive pathergy reaction, n (%)	2 (3.70)	2 (4.76)	0.797
BDCAF	3.00 (2.00-3.25)	3.00 (2.00-4.00)	0.986

BDCAF, Behçet's Disease Current Activity Form; $^{*}P < 0.05$.

Table 3. Preoperative laboratory indexes of the cardiac BS patients

	Favourable prognoses n=54	Unfavourable prognoses n=42	*P*
WBC, $\times 10^9$/L	8.70 (6.90-10.60)	8.4 (6.92-9.88)	0.515
Hb, g/L	126.00 (118.00-139.00)	121.00 (100.50-129.30)	0.146
PLT, ×109/L	214 (154.00-267.00)	175 (128.80-233.80)	0.254
NLR	4.13 (2.99-5.77)	2.191 (1.91-5.17)	0.314
ESR, mm/h	15.00 (8.75-23.25)	18.00 (10.00-50.00)	0.458
CRP, mg/L	8.05 (1.98-24.95)	31.50 (12.00-46.90)	0.007*

WBC, white blood cells; Hb, haemoglobin; PLT, platelets; NLR, neutrophil-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; *$P < 0.05$.

Table 4. Surgical procedures of cardiac BS patients

	Favourable prognoses n=54 (%)	Unfavourable prognoses n=42(%)	*P*
Surgical procedures			0.005*
Bentall procedure	26 (48.15)	8 (19.05)	/
Valve replacement or repairment operation	8 (14.81)	20 (47.62)	/
Concomitant aortic root replacement (except for Bentall)	2 (3.70)	2 (4.76)	/
Coronary stent implantation	4 (7.41)	2 (4.76)	/
Others (including non-operative patients)	14 (25.93)	10 (23.81)	/
The number of times of a certain surgery			0.655
Never	5 (9.26)	4(9.52)	/
First	30 (55.56)	27 (64.29)	/
Second	14 (25.93)	8 (19.05)	/
Third	3 (5.56)	3 (7.14)	/
Fourth	2 (3.70)	0 (0.00)	/

*$P < 0.05$.

Table 5. Immunosuppressive therapies for cardiac BS patients.

	Favourable prognoses n=54 (%)	Unfavourable prognoses n=42 (%)	*P*
Preoperative therapies			
Immunosuppressive therapies	31 (57.41)	8 (19.05)	0.000*
Oral steroid	27 (50.00)	7 (16.67)	0.001*
DMARDs	27 (50.00)	8 (16.67)	0.001*
JAK inhibiter	5 (9.26)	1(2.38)	0.339
Biological agent	7 (12.96)	2 (4.76)	0.310
JAK inhibiter or biological agent	12 (22.22)	3 (7.14)	0.044*
Postoperative therapies			
Immunosuppressive therapies	47 (87.04)	14 (33.33)	0.000*
Oral steroid	42 (77.78)	13 (30.95)	0.000*
Traditional DMARDs	45 (83.33)	11 (26.19)	0.000*
JAK inhibiter	13 (24.07)	3 (7.14)	0.027*
Biological agent	16 (29.63)	2 (4.76)	0.002*
JAK inhibiter or biological agent	29 (53.70)	5 (11.90)	0.000*
Poor compliance	5 (9.26)	25 (59.52)	0.000*

DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinases; *$P < 0.05$.

Table 6. Predictors of unfavourable prognoses in 96 cases of cardiac BS patients.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Erythema nodosum	0.47 (0.18-1.22)	0.122		
Pseudofolliculitis	1.78 (0.77-4.15)	0.181		
Exertional dyspnea	1.83 (0.72-4.64)	0.201		
Palpitation	0.22 (0.45-1.07)	0.060		
Current smoker	4.39 (1.42-13.59)	0.010*		
Former smoker	3.47 (1.48-8.14)	0.004*	8.17 (1.84-36.32)	0.006*
Current drinker	2.94 (0.82-10.55)	0.098		
CRP ≥ 31.50mg/L	10.78 (3.58-32.44)	0.000*		
Bentall procedure	0.25 (0.10-0.65)	0.004*		
Valve replacement or repairment operation	5.23 (1.99-13.71)	0.001*	13.49 (2.64-68.97)	0.002*
Concomitant aortic root replacement (including Bentall procedure)	0.31 (0.13-0.73)	0.008*		
Preoperative immunosuppressive therapies	0.18 (0.07-0.45)	0.000*	0.23 (0.06-0.90)	0.035*
Preoperative oral steroid	0.20 (0.08-0.54)	0.001*		
Preoperative DMARDs	0.20 (0.08-0.53)	0.001*		
Preoperative JAK inhibiter or biological agent	0.30 (0.08-1.16)	0.081		
Postoperative immunosuppressive therapies	0.07 (0.03-0.21)	0.000*	0.22 (0.05-0.95)	0.043*
Postoperative oral steroid	0.13 (0.05-0.32)	0.000*		
Postoperative DMARDs	0.07 (0.03-0.19)	0.000*		

Postoperative JAK inhibiter or biological agent	0.12 (0.04-0.34)	0.000*		
Poor compliance	14.41 (4.76-43.62)	0.000*	7.50 (1.42-39.62)	0.018*

*$P < 0.05$.

Table 7. Predictors of unfavourable prognoses in 65 aortic valve surgeries

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male gender	0.82 (0.25-2.68)	0.745		
Erythema nodosum	0.58 (0.17-1.96)	0.379		
Pseudofolliculitis	1.25 (0.44-3.59)	0.679		
Exertional dyspnea	1 (0.30-3.38)	1.000		
Palpitation	0.29 (0.06-1.50)	0.138		
Current smoker	3.88 (1.07-14.06)	0.039*		
Former smoker	2.95 (1.02-8.58)	0.047*	12.49 (1.04-149.94)	0.046*
Current drinker	1.64 (0.34-8.00)	0.540		
CRP ≥ 31.50mg/L	11.00 (2.21-54.67)	0.003		
Bentall procedure	0.11 (0.04-0.33)	0.000*	0.07 (0.01-0.78)	0.031*
Cardiac valve replacement	7.25 (2.31-22.73)	0.001*		
Concomitant aortic root replacement (including Bentall)	0.13 (0.04-0.38)	0.000*		
Preoperative immunosuppressive therapies	0.08 (0.02-0.28)	0.000*		
Preoperative oral steroid	0.12 (0.03-0.41)	0.001*		
Preoperative DMARDs	0.08 (0.02-0.33)	0.000*		
Preoperative JAK inhibiter or biological agent	0.14 (0.02-1.19)	0.072		
Postoperative immunosuppressive therapies	0.04 (0.01-0.20)	0.000*		
Postoperative oral steroid	0.04 (0.01-0.20)	0.000*		
Postoperative DMARDs	0.03 (0.006-	0.000*	0.02 (0.00-	0.002*

	0.15)		0.26)	
Postoperative JAK inhibiter or biological agent	0.07 (0.02-0.25)	0.000*	0.16 (0.03-0.94)	0.043*
Poor compliance	6.00 (1.18-30.62)	0.031*		

*$P < 0.05$.

Figures

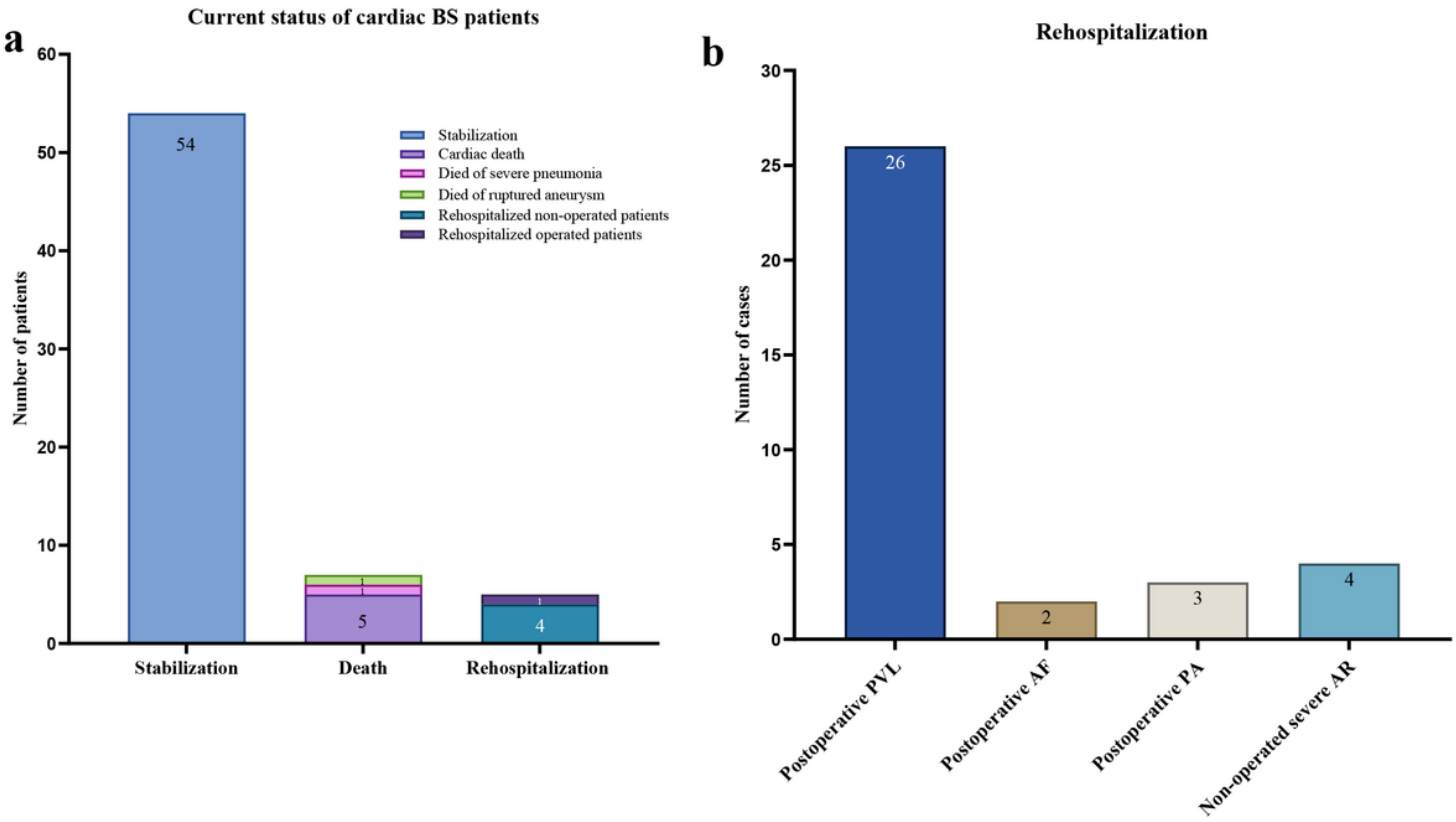

Figure 1

The outcomes of cardiac BS patients. a. The current situation of cardiac BS patients; b. The reasons for rehospitalization during the follow-up period. AF: arterial anastomosis fistula; PA: pseudoaneurysm.

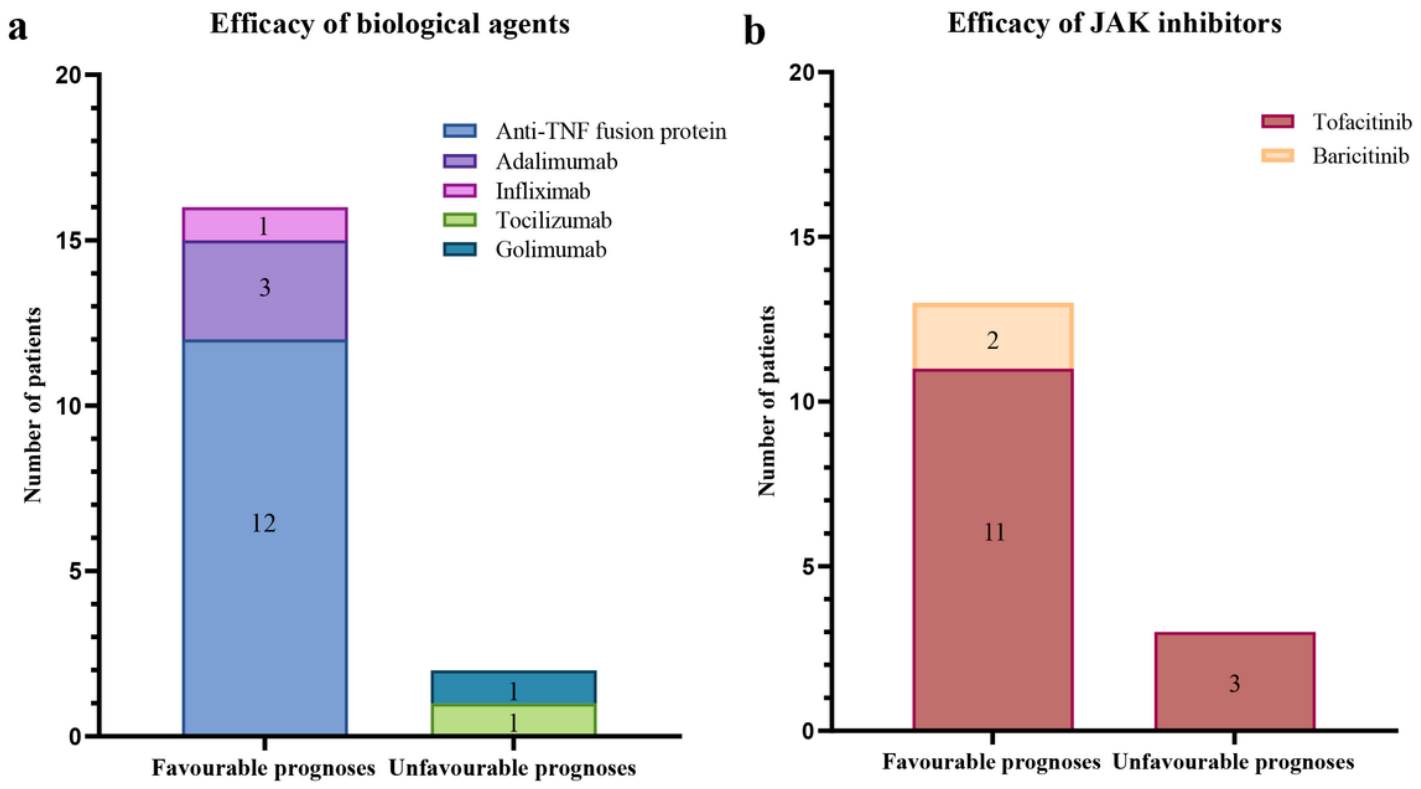

Figure 2

Efficacy of postoperative biological agents and JAK inhibitors. a. Efficacy of postoperative biological agents; b. Efficacy of postoperative JAK inhibitors.