Pediatric Behcet's Disease Patient with Cardiac Valvular Lesions: case report and a review of the literature

Xin Yao

Capital Institute of Pediatrics

Xin-Ning Wang

Capital Institute of Pediatrics

Zhi-Xuan Zhou

Capital Institute of Pediatrics

Sheng-Nan Li

Capital Institute of Pediatrics

Jianming Lai (✉ laijm99@sina.com)

Capital Institute of Pediatrics

Case Report

Keywords: Pediatric, Behcet's disease, Cardiac, Aortic valvular lesion, Infliximab

Posted Date: November 2nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1017088/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

To explore the clinical characteristics, treatment regimen, and prognosis of cardiac valvular involvement in pediatric Behcet's disease.

Methods

Retrospective analysis was conducted on the clinical data obtained from one pediatric patient suffering from Behcet's disease with cardiac valvular involvement. Present study also reviewed the literature related to cardiac involvement in pediatric Behcet's disease.

Results

The disease onset in the female patient was reported at the age of 3 years, with clinical symptoms, including aphthous ulcers, fever, perianal ulcers, and erythema nodosum, accompanied by a significant increase in the inflammatory markers. Echocardiography indicated that aortic valve (AV) lesions, which were absent initially, developed later, gradually exacerbated. Initially, she was diagnosed as "infectious disease" and "systemic inflammatory response syndrome", and antibiotic therapy proved ineffective. After an accurate diagnosis of Behcet's disease, the patient was given glucocorticoids, immunosuppressants, and biologics, which resulted in the relief of the symptoms; however, cardiac valvular lesions continued to exacerbate. Subsequent treatment included medical treatment and surgical treatment, and the patient's condition was stable at follow-up.

Conclusions

Cardiac valvular lesions in pediatric Behcet's disease are rare with insidious onset, enhancing the propensity of misdiagnosis or missed diagnosis. Main manifestations include recurrent oral ulceration, skin lesions, and fever. Cardiac involvement may occur early, yet the symptoms are insidious, requiring comprehensive physical examination and close monitoring of echocardiography. Glucocorticoids combined with immunosuppressants are the primary therapy for cardiac involvement in Behcet's disease. When cardiac valvular damage and dysfunction are observed, treatment regimens can be jointly recommended by multidisciplinary consultation to conduct the surgical treatment on time.

Background

Behcet's disease (BD) is a primary systemic vasculitis of unknown etiology, characterized by oral ulcers, genital ulcers, uveitis, and skin lesions, and may also indulge multi-system involvement, including blood vessels, gastrointestinal tract, joints, and nerves [1]. The prevalence of this disease is mostly observed in

countries along the Silk Road, with an incidence rate of 14–20/100,000 people [2]. BD involving the heart is referred to as cardiac Behcet's disease, include pericarditis, myocarditis, endocarditis, cardiac valvulopathy and et al, among which valvular involvement is rare, and misdiagnosis or missed diagnosis is extremely likely. The current study presented a case of pediatric Behcet's disease in our hospital, with cardiac valve lesions as the main manifestation. To comprehend the clinical basis of cardiac lesions in pediatric Behcet's disease, the relevant literature was also reviewed that could improve diagnosis and treatment of the condition.

Case Presentation

I. Presentation of Current Case

A 4-year-old female patient complained of experiencing recurrent oral ulceration (about once per month) 1 year prior to our hospital admission; no due attention was given at the disease onset.

10 months ago, she developed fever and accompanied by painful erythema nodosum on the dorsum of the left foot, bilateral distal lower extremities, and right ankle. During this period, the patient also experienced a perianal ulcer once and occasionally complained of fatigue, however, there was no abdominal pain, diarrhea, or ocular malaise. She was admitted to local hospital, and her laboratory tests were as follows: white blood cell (WBC): $15.5 \times 10^9/L$, C-reactive protein (CRP): 124 mg/L, erythrocyte sedimentation rate (ESR): 83 mm/H; positive results were obtained for both influenza A virus antigen and influenza B virus antigen; no abnormalities in autoantibodies (antinuclear antibody, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies), bone marrow cytology, electrocardiogram, or vascular ultrasound were noted. Minor signals of tricuspid regurgitation were detected in Color Doppler Echocardiography. She was initially treated medically with cephalosporin antibiotics and meropenem intravenous infusion therapy for over 20 days, without any improvement in the patient's symptoms. Subsequently, considering diagnose of "systemic inflammatory response syndrome", the child was given oral ibuprofen for 1 month (80mg each time, twice a day), during which the body temperature returned to normal, but oral ulcers and fatigue were still present.

5 months ago, during a visit for diarrhea, she was found a cardiac murmur from a doctor's auscultation. Further examining revealed the levels of N-terminal pro brain natriuretic peptide (NT-proBNP) was increased (1270 pg/mL), and severe aortic insufficiency, massive aortic regurgitation, the leaflets were thickened was observed via echocardiography, accompanied by gradual left ventricular enlargement and left cardiac systolic function reductio, ejection fraction (EF) 47-62% (Figure 1). Coronary ultrasound: expansion of the left coronary trunk (3.2 Z =+2.72). Chest radiography revealed the fullness of the pulmonary arterial segment with a cardiothoracic ratio of 0.54. 24-hour ambulatory Electrocardiograph (ECG) disclosed paroxysmal sinus tachycardia (mean heart rate 101 bpm, maximum heart rate 173 bpm), frequent atrial premature beat, and occasional trigeminy.

Two weeks prior to hospitalization, the patient experienced recurrent hyperpyrexia again and visited our hospital. Physical examination revealed chromatosis in bilateral distal lower extremities, grade 3/6 rumbling diastolic murmur at the cardiac apex (Austin-Flint murmur), New York Heart Association (NYHA) heart failure Class 2, and negative pathergy test. Prior physical health, growth, and development of the patient were found to be normal, and a family history of rheumatic diseases, tumor, or cardiovascular disorder was denied.

Evaluating the patient's medical history and the results of examination, a diagnosis of BD was considered (Diagnostic basis: 2 pt recurrent oral and perianal ulceration + 1 pt skin [erythema nodosum] + 1 pt vascular [coronary artery, cardiac valve] + others, including pyrexia and increased inflammatory indicators), in accordance with the 2013 The International Criteria for Behçet's Disease (ICBD) [3] and 2016 The Paediatric Behçet's Disease (PEDBD) classification criteria [4]. Taking into account the severe involvement of vital organs and progressive exacerbation, the patient was administered methylprednisolone tablets (1 mg/kg.d) and thalidomid oral, combined cyclophosphamide, infliximab (6 mg/kg) intravenous infusion therapy, while orally given diuretics for symptomatic treatment. After oral administration of glucocorticoids, the patient's body temperature returned to normal the next day; 1 week later, WBC, ESR, and CRP retests reverted to normal; whereas, 1 month later, NT-proBNP retest returned to normal. However, 2 months after regular treatment (the 14th month of the disease onset), echocardiography reports substantiated significant left cardiac enlargement, the posterior semilunar valve (non-coronary leaflets) prolapse, as well as damage to the anterior semilunar valve and right posterior semilunar valve (non-coronary leaflets) of the aortic valve, which signified a newly onset valvular impairment that was aggravating progressively. The patient underwent aortic valvuloplasty 15 months into the course of the disease. Following the operation, a significant decrease in aortic valve regurgitation was recorded (Figure 2). As of now, the patient has received regular treatment for 6 months, clinical symptoms disappeared, laboratory tests were all normal, and the patient's condition was stable.

II. Literature Review

A literature search of China national knowledge infrastructure (CNKI), Wanfang Data, and SinoMed (published before March 2021) with the keywords-"Behcet's", "cardiac", and "pediatric"- retrieved 1 relevant publication, reflecting 1 case of BD pediatric patient with comorbid multiple thrombi in the right cardiac chamber; There was currently no relevant reports on cardiac valvular involvement in pediatric BD.

With the search string "Behcet's, cardiac, pediatric", a literature search in Pubmed (published before March 2021) retrieved 55 publications. There were 13 publications closely related, all of which were published in the form of case reports. There were no large-scale case studies on cardiac involvement in pediatric BD.

A total of 14 cases of cardiac involvement in pediatric BD were summarized from 13 publications mentioned above. Among them, 13 males and 1 female, and the mean disease onset age was 11 ± 3.40 years (3 patients were 14, 17, and 15 years old, respectively when medical advice was sought, but the ages of the disease onset were unknown; therefore, only 11 cases were summarized with the known age of onset). Of the 14 patients, the longest time to diagnosis was 9 years; cardiac involvement was

observed at disease onset for 4 patients, 7 gradually developed cardiac symptoms during the course of the disease, while incidence time of cardiac involvement was not mentioned for 3. Two cases were misdiagnosed as infective endocarditis. Table 1 narrates details of clinical characteristics and other systemic involvement.

Among the 14 patients, cardiac involvement mainly reflected as: valvular lesions (2 cases), intracardiac thrombus (10 cases), coronary artery involvement (5 cases), myocardial infarction (2 cases), and ECG abnormality (2 cases); other comorbidities included ascending aortic aneurysm (2 cases), pulmonary artery involvement (4 cases), peripheral venous thrombosis (2 cases), and peripheral arterial thrombosis (1 case). Comorbid ECG abnormalities were reported in two cases, including 1 case with abnormal T waves and 1 case with successive ST changes, pathological Q wave, and inverted T waves. Pulmonary arterial hypertension was not reported. One case documented comorbid thrombosis in the superficial femoral vein, deep femoral vein, right hepatic vein, and inferior vena cava, 1 case reported comorbid superior vena cava thrombosis, and 1 case comorbid popliteal artery thrombosis (Table 2).

Glucocorticoids were given to all 14 patients, among them, 4 received pulse therapy. Twelve patients were treated with immunosuppressants, including cyclophosphamide (8 cases), colchicine (6 cases), mycophenolate mofetil (4 cases), azathioprine (3 cases), methotrexate (2 cases), and cyclosporin (1 case). Biologics, including infliximab (2 cases) and anakinra (1 case), were administered to three patients. Eight patients received surgical treatment, surgical resection of thrombus or aneurysm was conducted on 6 of them (5 patients recovered and the postoperative condition of one patient was unknown), and 1 underwent aortic valvuloplasty with autologous pericardium and recovered after 2 months. One patient underwent mitral valve repair and replacement as well as exclusion of aneurysms and catheter placement of occlusion devices in aneurysmal communications, however, the patient developed end stage heart failure. Orthotopic heart transplantation was performed, followed by maintenance therapy with cyclosporin, mycophenolate mofetil, and prednisone. The post-transplant course was complicated by periodic episodes of renal failure, recurrence of painful mouth ulcers, hypertension and several large pseudoaneurysms were found in the ascending aorta at the site of the surgical anastomosis. Emergency surgical re-anastomosis and exclusion of the aneurysm was performed without complication. The patient survived for > 2 years post-transplant at the time of the report, with no aneurysm regrowth [5]. (Table 3).

As per our literature search, the current case demonstrated the youngest age of disease onset reported in literature among pediatric BD with cardiac involvement and was the only case with aortic valve damage as the main clinical manifestation.

Discussion And Conclusions

The prevalence of BD is rare in children, accounting for 1.6-7.7% of all cases of this disease, and is more common among males [6–8]. Highly heterogeneous clinical manifestations of this disease and the lack of specific laboratory tests complicate the early diagnosis of pediatric patients. Several previous studies

also suggested variations in the clinical symptoms of pediatric BD from that of adults, such as more common gastrointestinal tract manifestations and less frequent ocular involvement than adults [9, 10]. In pediatric BD with cardiac involvement, oral ulceration is the most common clinical manifestation, followed by genital ulceration and skin lesions [4]. Considering the characteristics of the patient in the current study, including recurrent oral ulceration, perianal ulceration, and skin lesions, the clinical manifestations were in line with that reported in the relevant literature.

Cardiac involvement is relatively rare in BD and is usually associated with poor prognosis [11, 12] with a mortality rate of up to 20% [13]. In 2007, a retrospective analysis by the Peking Union Medical College Hospital of 348 BD cases discovered that the incidence rate of BD cardiac involvement was 12.1% [14]. As of now to date, the incidence rate of BD cardiac involvement in the pediatric population has not yet been reported. Cardiac involvement in BD mainly encompasses conduction disorders, endocardial fibrosis, intracardiac thrombosis, myocarditis, pericarditis, acute myocardial infarction, and cardiac valvular lesions. Heart valve disorders are comparatively rare in BD, with an incidence rate of 6-50% in adults [14, 15]. With an incidence rate up to 57.1% and 67.9%, aortic valve involvement is most commonly observed, frequently reflected as leaflet prolapse in the echocardiogram [18, 19], though the mitral valve and tricuspid valve may also be involved [16–19]. According to literature, the pathophysiology of valvular damage in BD involves extensive inflammation in the aorta and paravalvular tissue, indicated as small patches of necrotic lesions along with focal lymphocytic infiltration in pathological biopsy; the mitral valve may also be involved [19]. At the moment, only two case reports of cardiac valvular involvement in pediatric BD were documented, one being mitral and aortic valve vegetations and mitral leaflet damage [20], and the other being mitral annulus disruption with severe mitral insufficiency [5], with no reports related to aortic valve leaflet damage. The literature search in this study also revealed that cardiac involvement mainly manifested as intracardiac thrombus (10/14) and coronary artery involvement (5/14) in pediatric BD, while valvular involvement was less common (2/14), which differed from relevant large sample investigations in adults [21]. Characteristics of pediatric disease onset, population sample size, and/or regional differences may contribute to the possible reason behind such variation among adults and pediatrics. The patient's cardiac involvement in the present study was predominantly cardiac valvular lesions, which was a gradual shift from lesions in aortic valvular function to valvular structure, finally leading to irreversible damage to anterior semilunar valve and right posterior semilunar valve (non-coronary leaflet) of the aortic valve.

The severity of the disease and the site of organ involvement dictate the BD treatment [22]. Literature suggests that the primary disease should be the first target while treating cardiac involvement in BD, mainly with glucocorticoids combined with immunosuppressant therapy, whereas methylprednisolone pulse therapy or biologics can be considered whenever necessary [23]. Hatemi G et al. proposed the use of azathioprine in the management of BD with cardiac and pulmonary involvement [24]. In recent years, tumor necrosis factor α inhibitors, especially infliximab and adalimumab, have been increasingly applied to cure various refractory BDs, such as BD uveitis [25, 26], central nervous system involvement [27], intestinal Behcet's disease [28], and cardiac Behcet's disease [29]. A summary of the literature search documented that all 14 patients were treated with glucocorticoid therapy, while immunosuppressant

therapy (in descending order) included cyclophosphamide, colchicine, mycophenolate mofetil, azathioprine, methotrexate, and cyclosporin. Following treatment with adequate doses of glucocorticoids accompanied by cyclophosphamide and infliximab, the patient in the current study experienced lasting remission of symptoms, including pyrexia, rash, and oral ulcers, and CRP and ESR were maintained at normal levels. However, progressive exacerbation of irreversible valvular damage necessitated further surgical treatment. Whether was the patient eligible for surgery? How should the timing of the surgery be determined? Further research revealed an extremely high prevalence of paravalvular leak after aortic valve replacement in patients with comorbid BD valvular lesions who underwent surgical treatment during the active period of the disease [19]. Therefore, prior to surgery, it is strictly essential to control the primary disease [23], and post-procedural inflammation indicators should be maintained at low levels to minimize postoperative complications and avoid re-operation. Thus, the appropriate application of postoperative maintenance therapy with immunosuppressants is also crucial [30]. In this case, the patient received active Internal Medicine treatment for 3 months, she had no primary symptoms such as fever, oral ulcers, rash, perianal ulcers, and elevated inflammatory indicators. The sufficient remission provided conditions and opportunities for surgical procedures. After comprehensively assessed by specialists of rheumatology department and the cardiac surgery department, the patient had surgical indications, and the aortic valvuloplasty was successfully completed. After surgery, the patient was treated with sequential rheumatology treatment. The patient is currently 3 months post-surgery, and there are no surgery-related complications, abnormalities in monitored clinical symptoms, or laboratory tests.

To summarize, attributed to its insidious onset, early diagnosis of pediatric cardiac BD is difficult, resulting in misdiagnosis and missed diagnosis extremely likely, which may ensue delayed treatment of the illness, indicating poor prognosis. Active treatment for the primary disease and close monitoring of echocardiography must be ensured in pediatric patients with comorbid valvular involvement. Personalized treatment regimens should be jointly devised via multidisciplinary consultation to ameliorate prognosis.

Abbreviations

BD: Behcet's disease; AV: aortic valve; WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NT-proBNP: N-terminal pro brain natriuretic peptide; EF: ejection fraction; ECG: Electrocardiograph; NYHA: New York Heart Association; CNKI: China national knowledge infrastructure; CTX: cyclophosphamide; AZA: azathioprine; CsA: cyclosporine; MMF: mycophenolate mofetil; MTX: methotrexate

Declarations

Ethics approval and consent to participate

Parental informed consent for publication was obtained. This study was approved by the Ethics Committee of Capital Institute of Pediatrics.

Consent for publication

No applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This study is funded by Supported by Research Foundation of Capital Institute of Pediatrics (PY-2020-04).

Authors' contributions

YX wrote the first draft of the manuscript, contributed to patient management and to the literature review. Dr. WXN made many contributions in the process of writing and revising the manuscript. Prof. ZZX and LJM supervised patient management. Dr. LSN critically revised the manuscript and supervised patient management. All the authors read and approved the final version of the manuscript.

Acknowledgements

No applicable.

References

1. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet' disease. *N Engl J Med*. 1999;341: 1284–91.
2. Scherrer MAR, Rocha VB, Garcia LC. Behçet's disease: review with emphasis on dermatological aspects. *An Bras Dermatol*. 2017;92(4):452–464.
3. 2013ICBD 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.
4. Koné-Paut I, Shahram F, Darce-Bello M, et al. PEDBD Group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis*. 2016;75(6):958–64.
5. Hollander SA, Yasnovsky JR, Reinhartz O, Chan F, Sandborg C, Hunt S, et al. Behcet's disease and heart transplantation: a word of caution. *J Heart Lung Transplant*. 2010;29(11):1306–8.

6. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet*.1990;335(8697):1078–80.
7. Suzuki Kurokawa M, Suzuki N. Behcet's disease. *Clin Exp Med*. 2004;4(1):10–20.
8. Tursen U, Gurler A, Boyvat A. Evaluation of clinical findings according to sex in 2,313 Turkish patients with Behcet's disease. *Int J Dermatol*. 2003;42(5):346–51.
9. Ammann AJ, Johnson A, Fyfe GA, Leonards R, Wara DW, Cowan MJ. Behçet syndrome. *J Pediatr*. 1985;107(1):41–3.
10. Mori M, Shimizu C, Kuriyama T, Ibe M, Mitsuda T, Aihara Y, Yokota S. Behçet's disease in childhood—case reports and review of literature. *Ryumachi*. 1994;34(1):34–41.
11. Gürler A, Boyvat A, Türsen U. Clinical manifestations of Behçet's disease: an analysis of 2147 patients. *Yonsei Med J*. 1997;38(6):423–7.
12. Mogulkoc N, Burgess MI, Bishop PW. Intracardiac thrombus in Behçet's disease: a systematic review. *Chest*. 2000;118(2):479–87.
13. Wechsler B, Du LT, Kieffer E. *Ann Med Interne (Paris)*. 1999;150(7):542–54.
14. Liu Y, Tian Z, Fang L, Zeng X. Clinical characteristics of 42 Patients with heart damage in Behcet's disease. *Chinese journal of internal medicine*. 2007;46:537–40.
15. Gürgün C, Ercan E, Ceyhan C, Yavuzgil O, Zoghi M, Aksu K, et al. Cardiovascular involvement in Behcet'disease. *Jpn Heart J*. 2002;43(4):389–98.
16. Zheng W. Pay attention to the vascular lesions in Behcet's disease. *Chinese journal of rheumatology*, 2016;20(12):793–95.
17. Huang X, Huang C, Sha Y, Wang Q, Zeng X. Clinical analysis of 10 cases of Behcet's disease with valvular disease as prominent manifestation. *Chinese journal of medicine*, 2010;90(33):2357–59.
18. Gao N, Han W, Ci W, Liao H, Du J. Clinical characteristics of patients with cardiovascular involvement in Behcet's disease. *Chinese journal of medical science*. 2016;96(19):1523–25.
19. Zhao X, Wang H, Song M. Cardiovascular system damage in Behcet's disease: clinical data analysis of 28 cases. *Chinese journal of circulation*, 2014;29(3):213–15.
20. Kang HM, Kim GB, Jang W-S, Kwon BS, Bae EJ, Noh CI, et al. An adolescent with aortic regurgitation caused by Behcet's disease mimicking endocarditis. *Ann Thorac Surg*. 2013;95(6):e147-9.
21. Ghorbel IB, Belfeki N, Houman M H. Intracardiac thrombus in Behçet's disease. *Reumatismo*. 2016;68(3):148–153.
22. Endo LM, Rowe SM, Romp RL, Buckmaster MA, Atkinson TP. Pulmonary aneurysms and intracardiac thrombi due to Behcet's disease in an African-American adolescent with oculocutaneous albinism. *Clin Rheumatol*. 2007;26(9):1537–9.
23. Ando M, Okita Y, Sasako Y, et al. Surgery for aortic regurgitation caused by Behcet's disease: a clinical study of 11 patients. *J Card Surg*.1999;14:116–21.
24. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, et al. Management of Behcet disease: A systematic literature review for the European League Against Rheumatism evidence-based

- recommendations for the management of Behcet disease. *Ann Rheum Dis*. 2009;68:1528–34.
25. Tugal-Tutkun I, Mudun A. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. *Arthritis Rheum*. 2005;52(8):2478–84.
26. Wechsler B, Sablé-Fourtassou R, Bodaghi B, Huong DLT, Cassoux N, Badelon I, et al. Infliximab in refractory uveitis due to Behçet's disease. *Clin Exp Rheumatol*. 2004;22(4 Suppl 34):S14-6.
27. Sarwar H, McGrath Jr H, Espinoza LR. Successful treatment of long-standing neuro-Behçet's disease with infliximab. *J Rheumatol*. 2005;32(1):181–3.
28. Park YE, Cheon JH. Updated treatment strategies for intestinal Behçet's disease. *Korean J Intern Med*. 2018;33(1):1–19.
29. Jeong DS, Kim K, Kim JS, Ahn H. Long-term experience of surgical treatment for aortic regurgitation attributable to Behçet s disease. *Ann Thorac Surg*. 2009;87:1775–82.
30. Ding Y, Li C, Liu J, Shi J, Li L. Biological agents were used to treat 8 cases of Behcet's disease with valvular disease. *Chinese Journal of Clinical Immunology and Allergy*. 2019;2:108–12.

Tables

Due to technical limitations, Tables 1, 2 and 3 are only available as a download in the Supplemental Files section.

Figures

Figure 1

Echocardiography of the patient in the present study before surgery. Three leaflets in the aortic valve were identified by the Echocardiography. Fusion of the non-coronary leaflet with the root of the anterior semilunar valve was also evident; the leaflets were enhanced and thickened. Redundancy of the non-coronary leaflet resulted in prolapse into the left ventricular outflow tract and poor valve closure. Aortic insufficiency accompanied massive regurgitation. Lower normal left ventricular systolic function was indicated by 32% left-ventricular short-axis fractional shortening and 61% ejection fraction.

Figure 2

Echocardiography of the patient in the present study after surgery. Echocardiography suggested significantly lower aortic valve regurgitation than before.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.pdf](#)
- [Table2.pdf](#)
- [Table3.pdf](#)