Immunosuppression medication and cardiac function improvement treatments might prevent Takayasu arteritis patients with aortitis from receiving cardiac surgery

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To the Editor: Takayasu arteritis (TA), a non-specific large-vessel vasculitis characterized by granulomatous inflammation of vascular walls,[1] has been reported the main cause for 53% of aortitis.[2] TA with aortitis, involving aorta, aortic root (ring and sinus), and valves, may lead to heart failure and mortality attributed to aortic stenosis or dilation, aneurysm or dissection, aortic valve insufficiency, perivalvular leakage, and so on.[3] Medication treatments (glucocorticoids, traditional immunosuppressive agents and/or biological agents) are cornerstones for TA patients with aortitis, while part of them might further benefit from cardiac surgical treatments (aortic valve replacement [AVR], Bentall procedure, coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], etc). However, it is unclear about the prognosis of TA patients with aortitis. This study aimed to investigate their clinical outcomes and explore associated factors to guide healthcare practices.

Eligible candidates derived from participants of a living, ongoing and prospective TA registry study in the East China since 2009,[4] approved by the Ethics Committee of Zhongshan Hospital (No. B2016-168) and complied with the *Declaration of Helsinki*. They met the TA classification criteria of 1990 American College of Rheumatology, and were evaluated at baseline (demographics, manifestations, comorbidities, laboratory and radiological examinations, activity evaluation, etc) and followed up regularly. Patients with aortitis were included who satisfied: (1) imaging findings (including computed tomography angiography, magnetic resonance angiographic, positron emission tomography, and echocardiography); or (2) intra-operative visible findings (including congestion, edema, thickening, pseudoaneurysm, prolapse, tear, and/or perivalvular leakage); or (3) pathological findings (non-infectious inflammation in vascular and valvular tissues). Patients were excluded when having atherosclerosis, infection, tumor, rheumatic diseases, systemic vasculitis, or congenital heart diseases. In this study, the primary outcome was set that TA patients with aortitis accepted primary cardiac surgeries, while the secondary outcome was the occurrence of secondary cardiac surgeries (namely cardiac reoperation). Univariates of disease activity (evaluated by Kerr score), cardiac function (evaluated by 1928 New York Heart Association [NYHA] classification), medications, and examinations were compared between subjects with and without study outcomes. Multiple logistic regression analyses further determined independently associated factors with study outcomes (in forms of odds ratio [OR]). Kaplan-Meier curve was used to show time to outcomes. Clinical remission was defined as satisfying no new-onset nor aggravated manifestations, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) decreasing to normal, and glucocorticoid dose $\leq$15 mg/day.

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A total of 115 patients with TA and aortitis were enrolled [Supplementary Figure 1, http://links.lww.com/CM9/A362], with mean onset age of 39.9 ± 14.5 years and female accounted for 80.0%. Surgical fields indicated thickening (50.0%) and congestion (38.9%) in aortic wall, insufficiency (83.3%), thickening (38.9%), prolapse (38.9%) and ring enlargement (33.3%) in aortic valve, and thickening (55.6%), widening (44.4%), congestion (27.8%) in ascending aorta. At baseline, 101 (87.8%) were evaluated as active, while 82 (71.3%) of whom received immunosuppression medications including monotherapy of glucocorticoids ($n = 21$; mean dose: 31.4 ± 16.0 mg/d) and combined regimen of glucocorticoids and immunosuppression drugs ($n = 61$; including hydroxychloroquine [$n = 27$], cyclophosphamide [$n = 23$], leflunomide [$n = 15$], mycophenolate mofetil [$n = 12$], thalidomide [$n = 6$], azathioprine [$n = 4$], and methotrexate [$n = 3$]). Thirty-seven were evaluated as NYHA class I, 20 as class II, 53 as class III, and 5 as class IV. With a mean follow-up time of 39.1 ± 30.2 months, 66 (57.4%) cases attained both clinical remission and cardiac function of class I-II after receiving immunosuppression medications, among which 43 cases were active with class I-II and 23 cases were active with class III-IV originally. Other active patients with class III-IV included 16 attained remission but no cardiac function improvement after immunosuppression treatments and accepted cardiac surgeries finally, and 19 received cardiac surgeries directly without immunosuppression treatments. At the end of follow-up, 35 had primary outcomes of receiving primary cardiac surgeries (ten Bentall procedures, eight AVR, five aorta replacements, six CABG, two PCI, and one other bypass graft), among which five had secondary outcomes of receiving secondary cardiac surgeries (two PCI for restenosis, two AVR for perivalvular leakage, one aortic valve repair for valve perforation). One died from liver and kidney insufficiency within 30 days after surgeries. Sixteen continued post-operative immunosuppression medications, and 30 attained clinical remission and cardiac function improvement after 6 months post-operatively. Significant improvements were seen in levels of platelets, fibrinogen, ESR, CRP, internal diameter of aortic root, left ventricular end systolic diameter, posterior wall thickness of left ventricle, and ascending aorta width (all $P < 0.05$) [Supplementary Table 1, http://links.lww.com/CM9/A362].

Compared to patients without cardiac surgery, patients with at least one cardiac surgery were characterized by a higher rate of NYHA class III-IV (100.0% *vs.* 28.8%, $P < 0.001$), higher level of internal diameter of left atrium (45.5 ± 6.4 *vs.* 37.8 ± 3.9 mm, $P = 0.023$), and lower rate of receiving medication treatments (37.1% *vs.* 93.8%, $P < 0.001$) [Supplementary Table 2, http://links.lww.com/CM9/A362]. In multiple logistic regression analysis, NYHA class III-IV in cardiac function (OR = 6.7, 95%

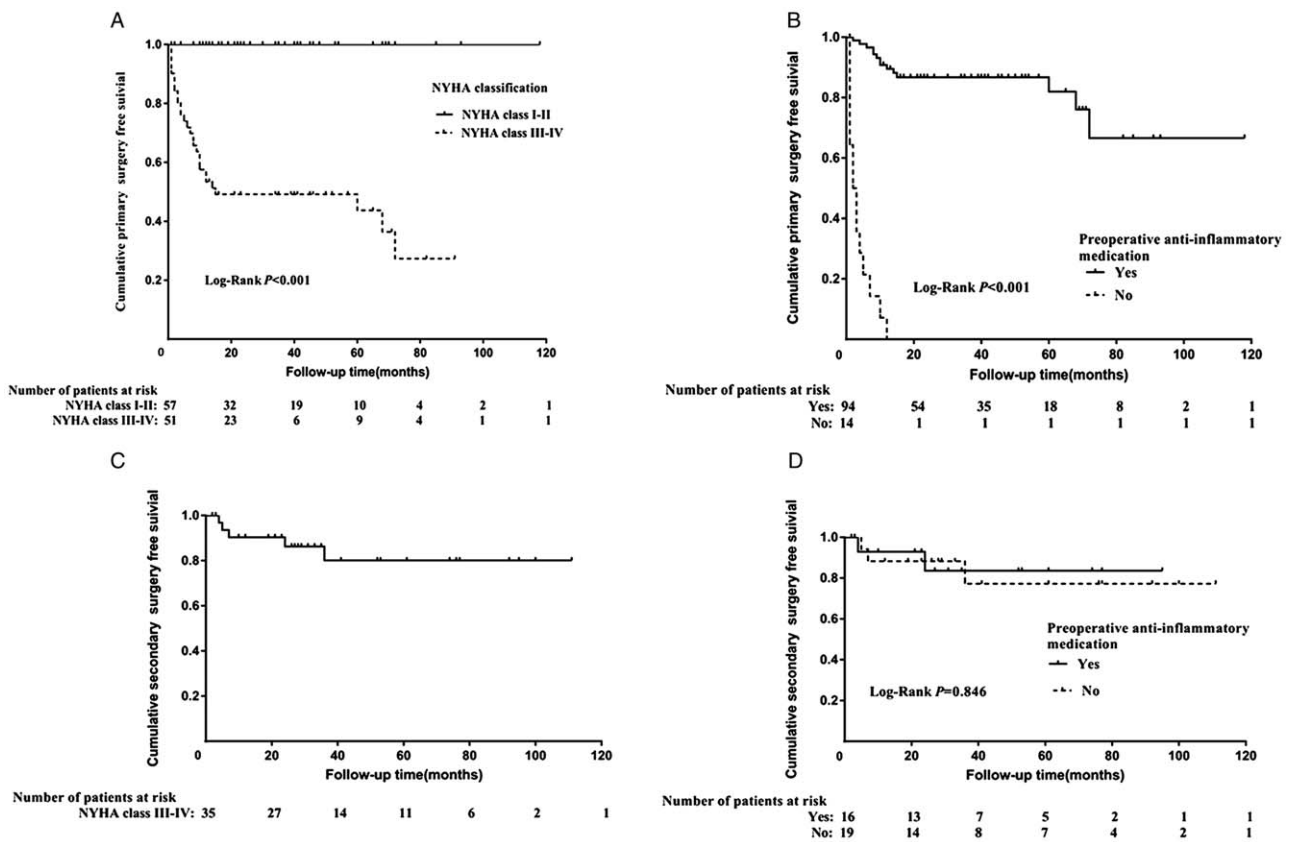

Figure 1: Kaplan-Meier plot of primary and secondary cardiac surgeries at follow-ups for Takara arteritis (TA) patients with aortitis. (A) For TA patients with aortitis, there was significant difference in cumulative primary surgery free survival between patients with NYHA class I-II and patients with class III-IV ($P < 0.001$). (B) A significant difference was indicated in cumulative primary surgery free survival between patients with pre-operative immunosuppression medication and patients without ($P < 0.001$). (C) All the patients receiving secondary cardiac surgery were at class III-IV. (D) There was no significant difference in cumulative secondary surgery free survival between patients with pre-operative immunosuppression medication and patients without ($P = 0.846$). NYHA: New York Heart Association classification.

confidence interval [CI]: 2.6–17.1, $P < 0.001$) was a risk factor for outcomes of primary cardiac surgery, while immunosuppression medication treatments (OR = 0.3, 95% CI: 0.1–0.5, $P < 0.001$) were protective factor. As shown in Figure 1A, patients with NYHA class III-IV were more likely to have primary cardiac surgery than patients with class I-II. Patients without immunosuppression medication all received primary surgeries in the first 12 months, significantly different from patients with medications [Figure 1B]. All the patients receiving secondary cardiac surgery were at class III-IV [Figure 1C], and patients with pre-operative immunosuppression medication did not differ from those without [Figure 1D].

Our study indicated 60.3% of active patients with NYHA class III-IV received cardiac surgeries at follow-ups, at risk of primary cardiac surgeries in the first 15 months and secondary cardiac surgeries 6 months after primary ones. The administration of immunosuppression medications was demonstrated to control disease activity, stabilize and/or improve cardiac function, and prevent or postpone primary cardiac surgeries especially for these active patients with NYHA class III-IV. The mean time of medication-to-remission was 4.7 ± 1.9 months, and medication-to-surgery was 11 months. Furthermore, pre-operative immunosuppression medication treatments significantly improved post-operative outcomes especially decreasing incidence of secondary surgeries. Thus, early and sufficient immunosuppression medication treatments may benefit TA patients with aortitis to obtain better outcomes by accomplishing dual remissions both in disease activity and in cardiac function.

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Conflicts of interest

None.

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