

Prognostic Factors for Aggravated Vascular Damage in Takayasu Arteritis

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Research article

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Abstract

Background. Takayasu arteritis is a rare disease characterized by inflammation in the aorta and its branches. Some patients were discovered to suffer the aggravated vascular damage (AVD), monitored by imaging techniques, even with the anti-inflammation treatment. But the overall characteristics and prognostic factors of AVD remained unclear yet.

Methods. From the living East China Takayasu arteritis cohort, patients who underwent at least two magnetic resonance angiography (MRA) examinations at Zhongshan Hospital from April 2009 to April 2019 were enrolled as the derivation cohort to describe the characteristics of AVD and explore the prognostic factors of AVD in MRA. An independent group of patients from May 2019 to July 2020 comprising the validation cohort were used to validate the nomogram formed by these prognostic factors.

Results. Among 235 enrolled patients, 69 patients (29.4%) suffered AVD with the median follow-up of 14 months. The limb arteries and vascular stenosis were the most common vascular location and manifestation of AVD respectively. Patients with AVD were younger, had higher complement 4 levels at baseline, and lower disease remission rate at 6 months. Cox regression analysis revealed that younger age (HR: 0.25-0.42, 95%CI: 0.09-0.91), higher CRP levels (HR = 2.57, 95%CI: 1.51–4.36) at baseline, and lower remission rate at 6 months (HR = 0.36, 95%CI: 0.21–0.64) were significant predictors. In the validation cohort of 65 patients, 19 cases had AVD. The predictive nomogram based on these factors achieved C-indices of 0.745 and 0.641 in the derivation and validation cohort respectively.

Conclusions. Totally, 29.4% of patients suffered AVD, which manifested as vascular stenosis in limb arteries mainly. Younger age, higher CRP at baseline, and lower disease remission rate at 6 months were prognostic factors for AVD.

Background

Takayasu arteritis (TA) is a rare chronic idiopathic inflammatory vascular disease that mainly affects the aorta and its branches. The vascular damage of these involved vessels manifest as vascular stenosis or occlusion, dilation or aneurysm, and vascular wall thickening, which can lead to ischemia of vital organs such as the heart, brain, and kidneys, or aneurysmal rupture, which seriously threatens the survival, quality of life, and influences the prognosis of TA patients [1]. At present, the primary treatment target in TA is to alleviate disease activity, but some patients experienced silent vascular progression, manifest as aggravated vascular damage (AVD) in essence, despite having minimal clinical evidence of disease activity [2]. Furthermore, the vascular progression promises high mortality rate [3]. However, the general characteristics of AVD in TA remains unclear yet.

AVD is the foundation of poor prognosis (e.g., disability, mortality) in patients with TA [3]. Identifying risk factors of AVD is imperative to achieve better therapeutic goals and outcomes. It has been reported that

Loading [MathJax]/jax/output/CommonHTML/jax.js d carotidynia are risk factors for TA relapse, instead of

vascular complications [4], indicating the inconsistency between disease activity and AVD. Another study showed that the Caucasian race and smoking are related to mortality in patients with TA [5]. But it is still elusive that which factors could predict or facilitate AVD in TA for the moment.

Dynamically and directly monitoring vascular evolution during treatment is not only important in evaluating disease status to adjust treatment strategies and improve outcomes, but also indispensable in discovering AVD timely and its prognostic factors. Multiple imaging methods can be used to monitor vascular changes in TA. A previous study showed that ultrasound can sensitively reflect changes in the vascular wall and lumen, as well as disease activity in the presence of contrast-enhancing agents [6]. However, the available superficial vascular locations restrict its utility. Non-invasive magnetic resonance angiography (MRA), which involves only a low exposure to radiation, is still the most important technique used to monitor angiographic aggravation in the whole body. Previous studies and guideline also confirmed the value of MRA in vascular lesions assessment and disease activity assessment in patients with TA [1, 2, 7, 8].

The present study was designed to depict AVD in TA based on MRA examination during follow-up, to identify prognostic factors associated with AVD, and to form a predictive nomogram with these factors for clinical use.

Methods

Study design

This study was based on the living ongoing prospective multicenter East China Takayasu arteritis cohort (Clinical trial No. NCT03893136) established since April 2009. Patients in the cohort were diagnosed with TA according to the classification criteria of the American College of Rheumatology 1990 [9]. Patients received regular evaluation and follow-up every 1 month in the acute phase and every 3–6 months in the remission phase. A professional and fixed team, comprised of rheumatologists and radiologists, was responsible for the disease assessment and follow-up. Clinical data were collected and recorded using a standard protocol, and was routinely monitored by a prespecified data manager.

Patients who underwent at least twice whole-body MRA examinations at Zhongshan Hospital Fudan University were eligible for the current study, whom enrolled from April 2009 to April 2019 were included as the derivation cohort, while patients from May 2019 to July 2020 comprised the validation cohort. Relevant clinical and imaging data was obtained.

The study protocol conformed to the Helsinki Declaration and was approved by the ethic committee of Zhongshan Hospital, Fudan University. Written informed consents were obtained from all patients prior to the enrollment.

Definitions

Vascular changes were monitored using whole-body MRA every 6 months in the center generally. Vascular lumen diameter and vascular wall thickness of the aorta and its main branches were evaluated and calculated as previously described [2]. Imaging types were classified according to the revised angiographic classification of the international TA conference in Tokyo (1996) based on the lesion distribution [10]. The AVD included at least one of the following criteria in the same layers between two examinations in MRA: i) the vascular wall thickness increased > 20%; ii) the diameter of the lumen increased or decreased by > 20% in dilated or narrowed lesioned locations, respectively; iii) the length of the lesioned area increased by > 20%; iv) new onset vascular lumen stenosis, or dilation. The imaging results were assessed in a blinded manner by two radiologists who were not aware of the treatment regimen. Dispute was resolved by discussion.

The time for the first MRA examination was defined as baseline while the study endpoint was the time when AVD observed, or the last examination performed. The characteristics mentioned in the manuscript, such as age, C4, CRP, *etc.*, were all referred to the value at baseline, while the drugs were referred to the prescription during follow-up unless especially indicated.

The outcome of the study was the AVD in MRA during follow-up, and the figures are shown in the **Supplementary Figure S1**.

Disease condition assessment

The disease activity was measured using the National Institute of Health (NIH) score, including: i) systemic symptoms; ii) vascular ischemic signs and symptoms; iii) elevated erythrocyte sedimentation rate (ESR; >20 mm/h); and iv) positive imaging findings. New onset or worsening of two or more criteria (NIH score ≥ 2) indicated an “active status” [11, 12]. Disease remission was defined as with no new/worsened systemic symptoms, no new/worsened vascular symptoms or signs, normal ESR levels and glucocorticoid dose ≤ 15 mg/day at 6 months. The disease severity was evaluated according to the TA severity scale as shown in **Supplementary Table S1**.

Intervention strategy

Generally, treatment strategy for TA includes an induction phase and a maintenance phase. In the induction phase, oral prednisone was started at a dose of 0.8-1.0 mg/kg/day; after 4 weeks, the dose was tapered gradually over 5 months to a maintenance dose of 0.1–0.2 mg/kg/day. Along with prednisone, one or more immunosuppressants (cyclophosphamide (CYC), methotrexate (MTX), azathioprine (AZA), leflunomide (LEF), or mycophenolate mofetil (MMF)) could be administered according to the physician's discretion. The dosages of the drugs were as follows: CYC, 0.5–0.75 g/m² (usually 0.8 g) intravenously every 4 weeks; MTX, 10–15 mg/week orally; AZA, 25–50 mg/day orally; LEF, 10–20 mg/day orally; and MMF, 1–2 g/day orally. Induction treatment lasted 6 months. Maintenance therapy was with MTX (10–15 mg/week, orally), AZA (25–50 mg/day, orally), LEF (10–20 mg/day, orally), or MMF (1-1.5 g/day, orally).

For patients with refractory or severe disease and those with recurrent disease during follow-up, biological (8mg/Kg intravenously, every 4 weeks), and TNF- α antibody

(adalimumab, 40mg subcutaneously, every 2 weeks) would be recommended.

Statistics

Continuous variables are presented as mean \pm standard deviation and median (interquartile range, IQR), and compared using a *t*-test and a *Wilcoxon* rank-sum test, respectively, according to their normality. Categorical variables are expressed as frequencies (percentages) and compared using the Chi-squared test. A univariate Cox regression analysis was employed to identify factors related to aggravated vascular imaging, among which factors with a *P* value of < 0.1 were included for multivariate Cox regression analysis to discover the independent prognostic factors. The Kaplan-Meier curves and nomogram were performed to further evaluate the clinical value of these factors. The concordance index (C-index) and calibration curves were used to validate the efficiency and accuracy of the predictive model formed by the prognostic factors. A higher C-index indicates better consistency between performance and predicted results. The power was 0.884 based on the enrolled patients at baseline. A *P* value less than 0.05 with the two-tailed test was considered significant. SPSS 26.0 and R 3.6.2 were used to perform statistical analyses and to generate graphs.

Results

Characteristics of patients

A total of 235 patients were enrolled, among whom 192 cases (81.7%) were female. The age of patients at baseline was 31.0 years (range 23.0–43.0 years), while the median follow-up period was 13 months. Fatigue (27.2%) and fever (10.0%) were the most common symptoms, while 34.6% and 33.8% of patients suffered pulselessness and vascular bruit, respectively. 205 (87.2%) patients were in active disease with NIH score ≥ 2 , which is consistent with the SUVmax value in the positron emission tomography-computed tomography (PET-CT) [13]. Type I and IV constituted the major imaging types, and the subclavian arteries were the most vulnerable. Vascular stenosis (97.9%) and wall thickening (75.3%) were the main manifestations. (Table 1, Fig. 1)

Approximately 8.5% of patients had received prednisone and immunosuppressants before the baseline. During follow-up, the initial prednisone dose was 30 (15–40) mg/day, which was tapered to 15.0 (10.0–15.0) mg/day at 6 months. 48.5% (114 cases) of patients received one kind of immunosuppressant, and LEF (47.5%) and CYC (30.0%) were the most frequently used immunosuppressants. 16.2% (24 cases) of patients were prescribed biological agents, including IL-6R antibody (9.8%) and TNF- α antibody (3.4%) (**Supplementary Table S3**).

After 6 months of treatment, disease remission was obtained in 81.7% patients. Disease activity (NIH score), as well as serum levels of ESR, C-reactive protein (CRP), complement 3 (C3), and complement 4 (C4) significantly decreased ($P < 0.01$) (Fig. 1).

The AVD during follow-up

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Totally, 69 cases in 235 patients (29.4%) suffered AVD with the median follow-up period of 14 months, which was not significantly different from that (13 months) in patients without AVD. Arteries which were most vulnerable to disease progression were the right subclavian artery (31 patients, 44.9%), left subclavian artery (27 patients, 39.1%), left carotid artery (9 patients, 13.0%), and right iliac artery (6 patients, 8.7%). The vascular stenosis progression was the most common AVD types (67 patients, 97.1%), among which three cases of new lesions, new stenosis instead of vascular thickening or dilation in limb arteries, were observed in three patients. (Supplementary Table S2, Supplementary Figure S1).

Comparison of characteristics between patients with and without AVD

There was no significant difference in disease course, follow-up period, disease severity, symptoms (e.g., fatigue), and signs (e.g., vascular bruit, pulseless) between patient with and without AVD at baseline. Patients with AVD had lower median age, but higher frequency of fever (Table 1). Higher frequency of prednisone prescription history (10 cases, 14.5%) was observed in patients with AVD compared with that in patients without AVD (10 cases, 6.1%) at baseline. However, the dose of prednisone at baseline and 6 months showed no difference between two groups. The prescription of MMF (12 cases, 18.5%) and IL-6R antibody (12 cases, 18.5%) was more commonly seen in patients with AVD during follow-up (Supplementary Tables S3).

At baseline, patients with AVD had significantly higher C4 levels ($P < 0.05$), but the active disease status (NIH score ≥ 2), together with levels of ESR, CRP, interleukin (IL)-6, IL-8, C3, and CH50, showed no significant difference between two groups. However, compared with patients with AVD, patients without AVD had higher disease remission rate at 6 months after treatment (88.2% vs. 66.7%, $P = 0.001$) and lower percent of high CRP (≥ 26.7 mg/L) (22.3% vs. 42.6%, $P = 0.002$) respectively. (Table 1)

Prognostic factors of AVD

The univariate Cox regression analysis revealed that AVD was negatively associated with age and disease remission at 6 months ($P < 0.05$), but positively associated with CRP levels, C4 levels, and use of MMF and IL-6R antibodies ($P < 0.05$). And further stratification analysis of age (cut-off value: 18, 40 years), CRP (cut-off value: 26.7 mg/L) and C4 (cut-off value: 0.19, 0.29 g/L) also revealed the same tendency. However, disease severity, fever, ESR, IL-6, IL-8, C3, CH50, and dosage of prednisone at baseline were not associated with AVD ($P > 0.05$; Table 2).

After adjusting for C4 and the usage of IL-6R antibody as well as MMF, age (HR < 0.5 , $P < 0.05$) and disease remission rate at 6 months [HR (95%CI): 0.365 (0.210–0.636), $P < 0.001$] were negatively associated with AVD, while high CRP levels (> 26.7 mg/L) was positively associated with AVD [HR (95%CI): 2.566 (1.509–4.364), $P = 0.012$] in the multivariate Cox regression analysis (Table 3). The Kaplan-Meier curves also revealed that patients with higher age, lower CRP level, and higher disease

remission at 6 months instead of receiving IL-6R antibody or MMF treatment, had lower incidence of AVD during follow-up (Fig. 2, **Supplementary Figure S2**)

Predictive value of the nomogram based on prognostic factors

Based on the prognostic factors from multivariate Cox regression, the nomogram was generated. The C-index of the nomogram was 0.745. The 1- and 3-year calibration curves for the nomogram showed the consistency between the prediction and observation (Fig. 3A–C).

In the validation cohort comprised of 65 cases, 19 patients suffered AVD with the median follow-up of 8 months, shorter than that in the derivation cohort. There was no significant difference between two cohorts in terms of age, gender, disease course, signs, and disease severity at baseline. Patients in the validation cohort had lower levels of ESR, CRP, C3, and disease activity (NIH score ≥ 2) with a shorter follow-up period. However, the validation cohort still revealed the consistency in the prediction and observation in 1- and 2-year calibration curves, with a C-index of 0.641 in the nomogram (**Supplementary Table S4**, Fig. 3D and E).

Discussion

Multiple reports have employed angiographic changes as important indices for evaluating therapeutic effect, but the overall conditions of vascular progression remain obscure [14, 15]. According to the present study, about one third of patients with TA suffered AVD with the median follow-up of 14 months. The most common AVD type was aggravated vascular stenosis in the original lesioned locations, while new lesions were relatively less. The limb arteries were the most vulnerable locations, although the harm arising from limb artery lesions is likely to be less than that of critical arteries that govern vital organs such as the heart, brain, or kidneys, which could increase the likelihood of serious cerebrovascular adverse events and magnify the risk of mortality [4]. Considering the difference in vascular structure and locations between limb arteries and arteries supplying vital organs, hemodynamics such as sheer press and turbulent flow might be another critical issue resulting in aggravated vascular findings, which warrants further investigation. However, the choice of therapeutic strategy should be based on end-organ perfusion for the moment [16].

Assessment and intervention of inflammation are important in patients with TA [17]. ESR and CRP, together with SUVmax in PET-CT, increased in the active disease status, which is consistent with previous findings [13]. However, inflammatory markers at the baseline, including ESR, IL-6, C3, and IL-8, did not predict AVD. Disease remission after 6 months of treatment significantly improved outcomes, indicating that active, early, and successful intervention to control inflammation and disease activity are crucial in patients with TA.

Interestingly, C4 and CRP were related to angiographic aggravation. The complement system is tightly related to the pathogenesis of ANCA-associated vasculitis [18, 19]. In TA, complement components, such

as complement 4-binding protein and C3 [20, 21], can be used as biomarkers to monitor disease activity. In the present study, C4 was a risk factor for progression in vascular imaging, indicating that complement activation might be involved in the pathogenesis of TA. Although it was not an independent risk factor, which might be due to the limited sample size or to the confined function of C4 in complement activation, its valuable role in inducing vascular deterioration deserves further investigation.

CRP has been used as an acute phase protein to evaluate disease activity in TA during follow-up [20, 22, 23]. In the present study, CRP was found to be a prognostic factor for AVD. Comarmond et al. found that CRP, together with the male sex and carotidynia, was an independent risk factor for disease relapse [4], which is consistent with the result of present study since inflammation recrudescence is the essence of disease relapse and failure to alleviate disease activity might result in AVD. Moreover, the value of CRP instead of ESR or IL-6 in predicting AVD, also implied that CRP might be involved in the pathogenesis of TA in a deeper level from the perspective of molecular mechanisms, although the function of CRP in inflammation remains unknown largely yet [24].

Anti-inflammatory therapy is an art, especially anti-cytokine treatment, which partially interrupts vascular progress [25]. In the present study, we found that the patients in the AVD group were prescribed with more active intervention such as the usage of IL-6R and TNF- α antibodies. Previous investigations have shown that IL-6R antibody is effective for the treatment of refractory TA, and is better than cyclophosphamide [22, 23]. However, we found that some specific intervention such as IL-6R antibody failed to completely block the AVD currently, possibly because the disease condition in the progressive group was more severe, considering their younger age, higher C4, and resistance to active disease mitigation. Thus, more aggressive treatment strategies should be encouraged to obtain disease remission in the early stage of 6 months' treatment, regardless of the drug types.

Different from giant cell arteritis, TA usually starts at a young age [26]. In the present study, we found that younger age could further increase the risk of vascular poor prognosis, which is consistent with a previous report that IL-17 and the relapse rate decrease in patients with TA over the age of 40 years [27]. This might be because of immune aging and the abnormal differentiation of inflammatory cells, such as T-helper 17 cells, in elderly patients [27, 28]. Further investigations are needed to clarify the exact mechanisms. However, the claim that younger patients should be given active and effective intervention at early stage is affirmative.

The nomogram developed based on the prognostic factors was reliable not only in general new patients but in extreme conditions where patients received effective treatments and achieved therapeutic effects. Thus, the nomogram based on earlier characteristics of patients would be a useful tool to predict AVD in TA, implying the poor prognosis in the future. More precise intervention could be prescribed to obtain better prognosis according to hazard ratios obtained from the nomogram.

The present study has several limitations. First, the result has not been validated in TA patients from other cohorts. Second, the follow-up period of the validation was restricted, despite the agreement Loading [MathJax]/jax/output/CommonHTML/jax.js 2 years. Third, the present study focused on the AVD at the

whole level, further analysis of new lesions and different extent and locations of AVD could be performed dynamically based on the Angiographic Scores System created by Enrico Tombetti *et al.* [29]. Moreover, the relationship between AVD and different long-term prognosis of TA warrants further investigation.

In conclusion, 29.4% of patients in TA suffered AVD, which manifested as vascular stenosis in limb arteries mainly. Successful disease remission at 6 months, lower CRP (CRP \leq 26.7 mg/L), and higher age were protective factors for AVD in TA, on which the nomogram based provided a useful tool to predict AVD. Early and active intervention is important to reduce AVD, especially for young patients.

Abbreviations

AVD, aggravated vascular damage; AZA, azathioprine; CRP, C-reactive protein; CYC, cyclophosphamide; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; MMF, mycophenolate mofetil; MTX, methotrexate; LEF, leflunomide; HR, hazard ratio; IQR, interquartile range; MRA, magnetic resonant angiography; NIH, National Institute of Health; TA, Takayasu arteritis;

Declarations

Ethics approval and consent to participate. The study was approved by the ethic committee of Zhongshan hospital, Fudan University. Written informed consents were obtained when patients were enrolled in the prospective ongoing East China Takayasu arteritis (ECTA) cohort (NCT03893136).

Consent for publication. All participants provided written informed consent prior to their involvement, and the consent for publication has been acquired.

Availability of data and materials. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. Study design: Chen RY, Ma LL, and Jiang LD; Data acquisition and analysis: Chen RY, Ma LY, Liu Y, Lin J, Chen CZ, Wu SF, and Yu WS; Manuscript drafting and revising: Chen RY, Sun Y, and Jiang LD.

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Tables

Table 1. Demographic and clinical characteristics of patients with and without AVD at baseline.

| | Total (n = 235) | Without AVD (n = 166) | With AVD (n = 69) | P value |
|--|----------------------------------|--|------------------------------------|--------------------------|
| General data | | | | |
| Age, years | 31.0 (23.0 – 43.0) | 33.0 (23.8 – 45.0) | 27.0 (22.0 – 37.5) | 0.014* |
| Female, n (%) | 192 (81.7) | 139 (83.7) | 53 (76.8) | 0.211 |
| Disease course, months | 13.0 (3.0-51.0) | 14.0 (3.0-57.8) | 13.0 (2.5-45.5) | 0.917 |
| Follow-up period, months | 13.0 (7.0-29.0) | 13.0 (6.8-30.0) | 14.0 (7.0-28.0) | 0.725 |
| Symptoms and signs | | | | |
| Fever, n (%) | 23 (10.0) | 12 (7.4) | 11 (16.2) | 0.041* |
| Fatigue, n (%) | 64 (27.2) | 45 (27.1) | 19 (27.5) | 0.980 |
| Neck pain, n (%) | 12 (5.3) | 7 (4.4) | 5 (7.5) | 0.355 |
| Abdominal pain, n (%) | 6 (2.7) | 4 (2.5) | 2 (3.0) | 0.853 |
| Claudication, n (%) | 10 (4.3) | 7 (4.3) | 3 (4.4) | 0.968 |
| Pulselessness, n (%) | 80 (34.6) | 56 (34.4) | 24 (35.3) | 0.891 |
| Vascular bruit, n (%) | 78 (33.8) | 58 (35.6) | 20 (29.4) | 0.366 |
| Disease Severity, n (%)[†] | | | | |
| Mild | 44 (18.8) | 34 (20.6) | 10 (14.5) | |
| Moderate | 76 (32.5) | 47 (28.5) | 29 (42.0) | |
| Severe | 114 (48.7) | 84 (50.9) | 30 (43.5) | 0.118 |
| Disease remission at 6 months, n (%) | 161 (81.7) | 120 (88.2) | 41 (67.2) | 0.001* |
| Imaging Type, n (%) | | | | |
| I | 58 (24.7) | 45 (27.1) | 13 (18.8) | |
| IIa | 15 (6.4) | 10 (6.0) | 5 (7.2) | |
| IIb | 23 (9.8) | 18 (10.8) | 5 (7.2) | |
| III | 8 (3.4) | 5 (3.0) | 3 (4.3) | |
| IV | 22 (9.4) | 13 (7.8) | 9 (13.0) | |
| V | 109 (46.4) | 75 (45.2) | 34 (49.3) | 0.556 |
| Loading [MathJax]/jax/output/CommonHTML/jax.js (%) | | | | |

| | | | | |
|--|------------------|------------------|------------------|--------|
| Vascular wall thickening | 177(75.3) | 123(74.1) | 54(78.3) | 0.500 |
| Vascular stenosis | 230(97.9) | 163(98.2) | 67(97.1) | 0.632 |
| Simple aneurysm | 5(2.1) | 3(1.8) | 2(2.9) | 0.632 |
| Laboratory results (Baseline) | | | | |
| ESR, mm/H | 34.5 (15.0-63.0) | 34.5 (15.8-63.5) | 34.5 (14.0-60.5) | 0.568 |
| CRP, mg/L | 10.0 (2.1-30.9) | 9.0 (2.2-24.4) | 15.9 (2.0-50.3) | 0.107 |
| High CRP (> 26.7mg/L), n (%) | 66(28.2) | 37(22.3) | 29(42.6) | 0.002* |
| IL-6, pg/mL | 5.1 (2.2-11.8) | 4.6 (2.2-10.5) | 6.7 (2.1-17.7) | 0.281 |
| C3, g/L | 1.16 (1.02-1.34) | 1.15 (1.02-1.32) | 1.20 (1.00-1.40) | 0.417 |
| C4, g/L | 0.24 (0.19-0.28) | 0.23 (0.19-0.28) | 0.27 (0.21-0.31) | 0.009* |
| CH50, g/L | 67.3 (54.1-78.2) | 67.2 (52.3-77.9) | 67.6 (58.0-80.3) | 0.144 |
| NIH Score ³ 2, n (%) | 205 (87.2) | 144 (86.7) | 61 (92.4) | 0.313 |

Notes.

1. Abbreviations: AVD, aggravated vascular damage; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; C3, complement 3; C4, complement 4; CH50, median haemolytic complement. NIH, national institute of health.
2. The high CRP refers to the cases with CRP>26.7mg/L in the binary conversion of CRP values, with the cut-off value of 26.7mg/L.
3. **P*-value < 0.05 was considered to indicate statistical significance.
4. †Detailed description of disease severity scale is listed in Supplementary Table 1.

Table 2. Univariate Cox regression analysis for factors associated with AVD.

| | HR (95%CI) † | Pvalue |
|---|-------------------------|--------|
| Age | 0.977 (0.957-0.997) | 0.023* |
| 19~40 vs 0~18 ‡ | 0.423 (0.211-0.848) | 0.015* |
| 41~80 vs 0~18 ‡ | 0.288 (0.127-0.654) | 0.003* |
| Sex | 1.340 (0.762-2.335) | 0.309 |
| Disease course | 1.000 (0.997-1.003) | 0.827 |
| Fever | 1.715 (0.896-3.284) | 0.103 |
| Neck pain | 2.088 (0.830-5.252) | 0.118 |
| Fatigue | 0.856 (0.499-1.471) | 0.574 |
| Pulselessness | 1.165 (0.702-1.933) | 0.554 |
| Vascular bruit | 0.739 (0.437-1.252) | 0.261 |
| Severity | | |
| Moderate vs. mild | 1.099 (0.520-2.326) | 0.804 |
| Severe vs. mild | 1.815 (1.082-3.043) | 0.024* |
| Disease alleviation at 6 months | 0.412 (0.239-0.710) | 0.001* |
| Hb | 1.000 (0.987-1.013) | 0.987 |
| WBC | 0.995 (0.927-1.068) | 0.886 |
| PLT | 1.002 (1.000-1.014) | 0.082 |
| A | 0.996 (0.936-1.061) | 0.912 |
| G | 1.018 (0.974-1.063) | 0.432 |
| Disease activity (NIH score ³ 2) | 1.373 (0.591-3.188) | 0.461 |
| ESR | 0.998 (0.989-1.006) | 0.589 |
| CRP | 1.010 (1.004-1.017) | 0.001* |
| CRP > 26.7 vs CRP ≤ 26.7 ‡ | 2.335 (1.436-3.796) | 0.001* |
| IL-6 | 1.008 (0.993-1.023) | 0.294 |
| IL-8 | 0.998 (0.990-1.005) | 0.554 |
| C3 | 1.718 (0.517-5.710) | 0.377 |
| | 83.280 (1.440-4815.410) | 0.033* |

| | | |
|-----------------------|---------------------|--------|
| 0.20~0.29 vs 0~0.19 ‡ | 1.276 (0.653-2.494) | 0.477 |
| 0.30~0.49 vs 0~0.19 ‡ | 2.252 (1.091-4.648) | 0.028* |
| CH50 | 1.004 (0.989-1.018) | 0.641 |
| Previous prednisone | 0.928 (0.470-1.834) | 0.830 |
| Prednisone | 0.473 (0.065-3.419) | 0.458 |
| MMF | 0.582 (0.309-1.096) | 0.094* |
| IL-6R Ab | 0.421 (0.223-0.795) | 0.008* |

Notes.

1. Abbreviations: AVD, aggravated vascular damage; Hb, hemoglobin; WBC, white blood cells; PLT, platelet; A, albumin; G, globin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; C3, complement 3; C4, complement 4; CH50, median haemolytic complement; MMF, Mycophenolate Mofetil; IL-6R, interleukin-6 receptor.
2. * $P < 0.05$.
3. † Hazard ratio (HR) was calculated by “with the issue” (equal to 1) compared to “without the issue” (equal to 0) unless indicated in the table on the binary variable.
4. ‡ The variables were processed as the categorical variable according to the stratification.

Table 3. Multivariate Cox regression analysis for factors related to AVD.

| | HR (95% CI) | P value |
|--------------------------------------|---------------------|---------|
| Age | | |
| 0~18 (Reference) | | |
| 19~40 | 0.419 (0.192-0.913) | 0.029* |
| 41~80 | 0.246 (0.094-0.644) | 0.004* |
| Disease remission at 6 months | 0.365 (0.210-0.636) | <0.001* |
| CRP | | |
| CRP 26.7 (Reference) | | |
| CRP > 26.7 | 2.566 (1.509-4.364) | 0.001* |

Notes.

1. Abbreviation: AVD, aggravated vascular damage; CRP, C-reactive protein.

2. * $P < 0.05$.

Figures

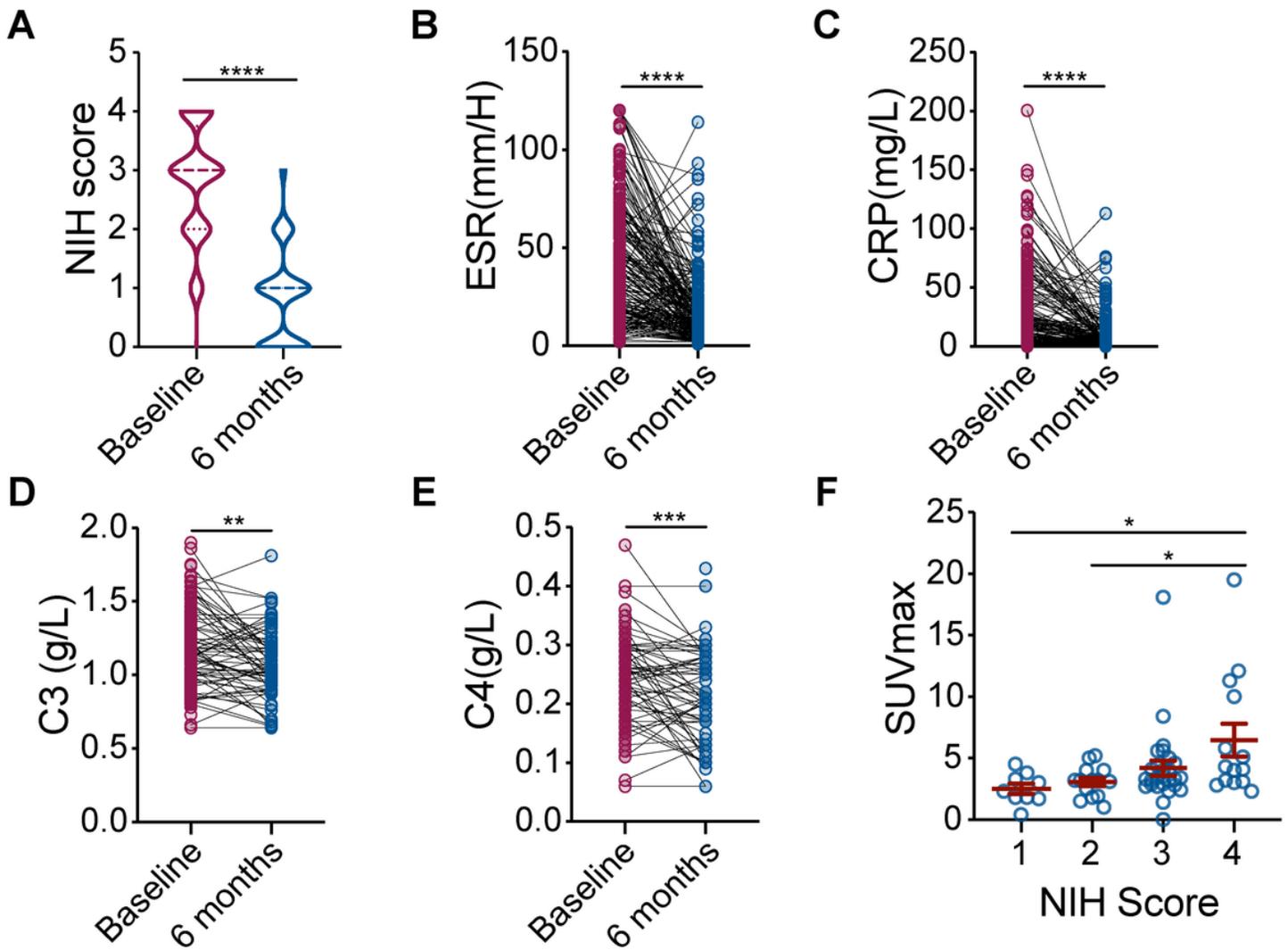


Figure 1

Changes in inflammatory markers after 6 months of treatment, and the relationship between NIH score and SUVmax by PET-CT at baseline. (A) The change in NIH score at 6 months of follow-up. (B-E) The change in ESR, CRP, C3, and C4 after 6 months of follow-up. (F) The distribution of SUVmax in PET-CT at baseline (original state) at different NIH scores. Notes. a. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. b. Abbreviations: NIH, National Institute of Health; SUVmax, maximum standardized uptake value; PET-CT, positron emission tomography-computed tomography; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; C3, complement 3; C4, complement 4.

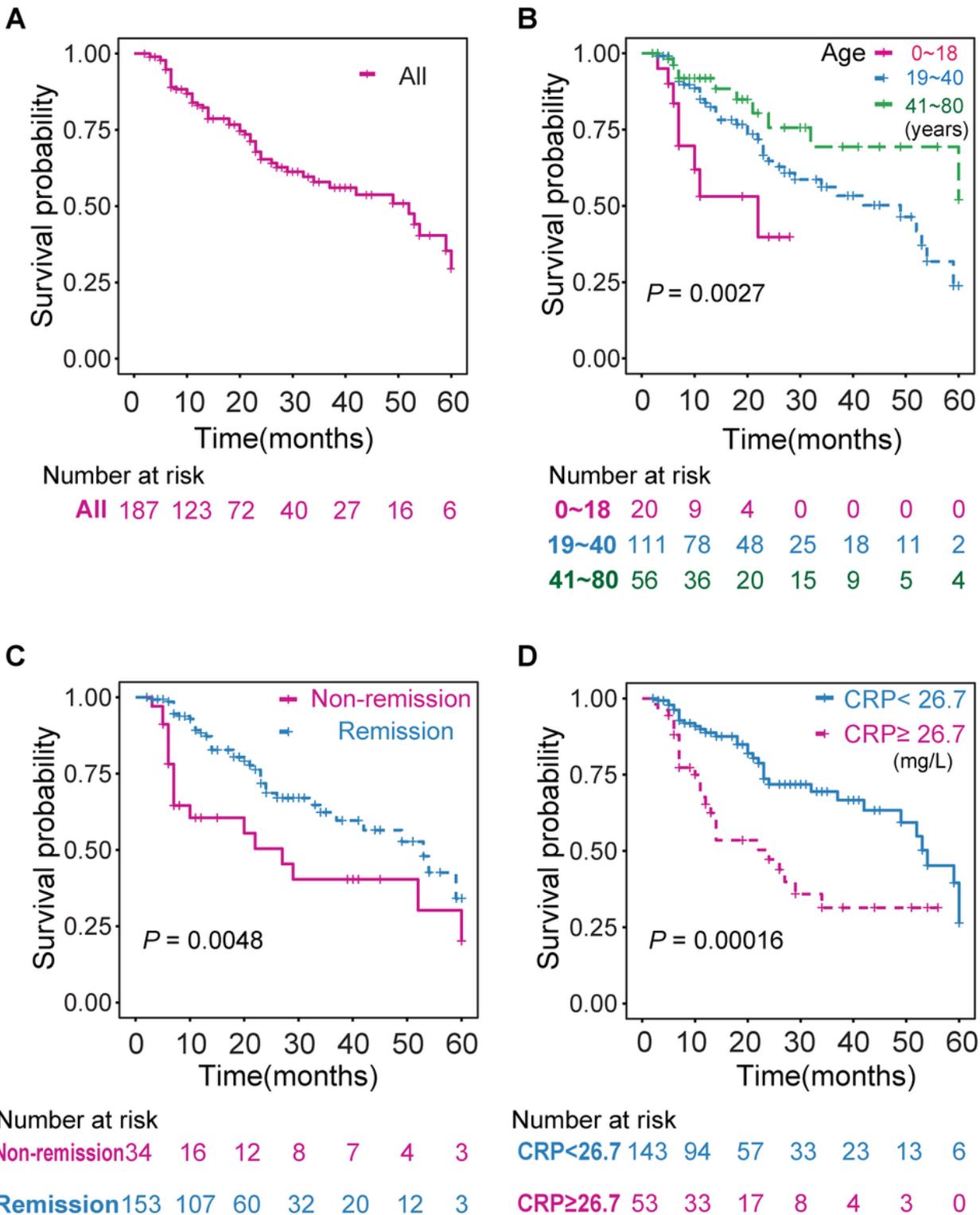


Figure 2

Kaplan-Meier curves of different items for aggravated vascular damage (AVD) in TA. (A – D) The Kaplan-Meier curves of the overall, different age stratifications, disease remission status, and CRP stratification for AVD in TA. Notes. a. TA, Takayasu arteritis; CRP, C-reactive protein.

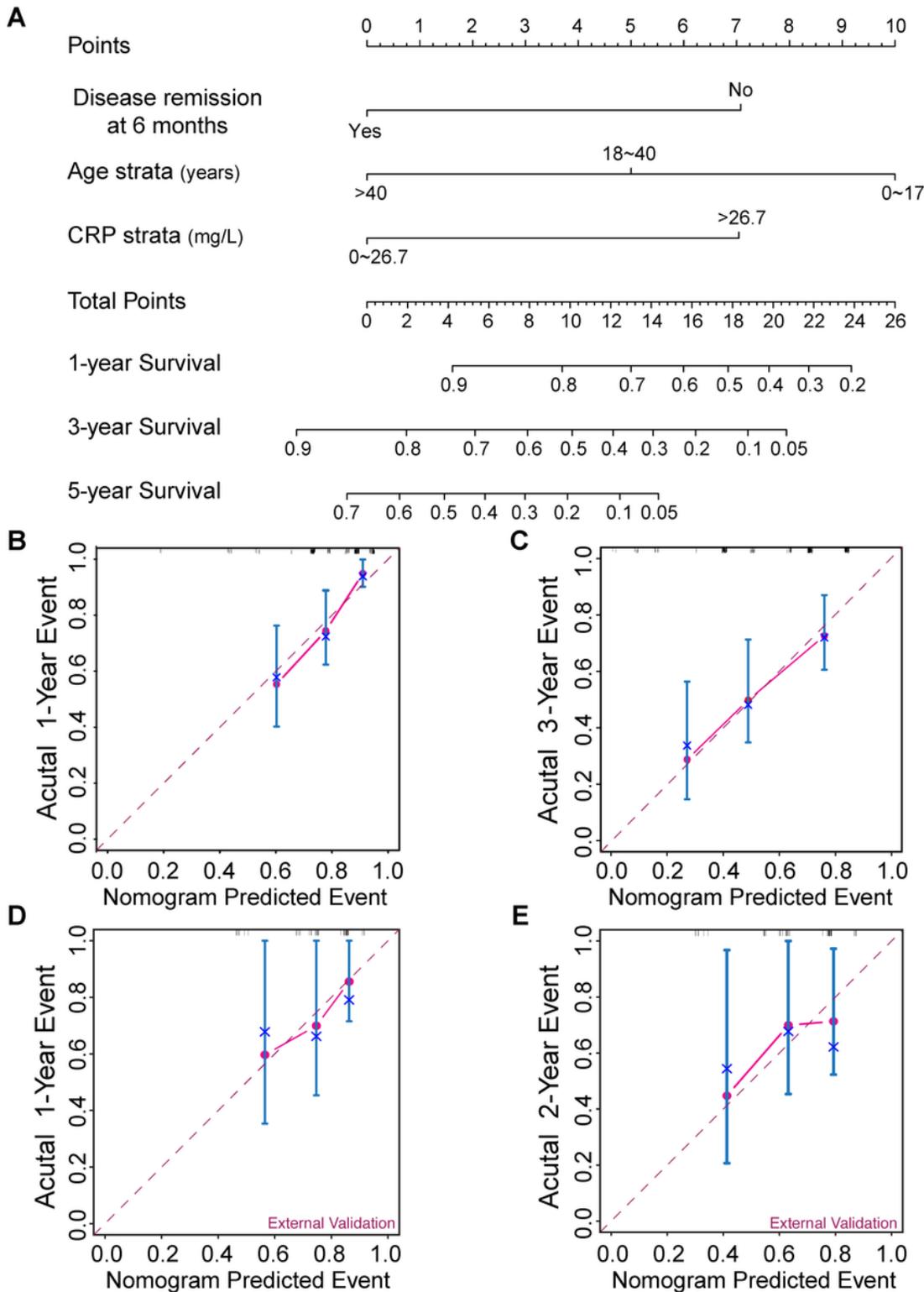


Figure 3

Nomogram and calibration curves of prognostic factors predicting aggravated vascular damage (AVD). (A) The prediction model of nomogram. (B – C) Calibration curves of nomogram for predicting AVD in the derivation cohort at 1 year and 3 years. (D – E) Calibration curves of nomogram for predicting AVD in the validation cohort at 1 year and 2 years.

Supplementary Files

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- [SupplementaryMaterials.docx](#)