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Anemia in patients with Takayasu arteritis: prevalence, clinical features, and treatment

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Abstract

Background Anemia is a common comorbidity of patients with Takayasu arteritis (TA). This study evaluated the prevalence, clinical characteristics, and treatment in Chinese TA patients with anemia. **Methods** This retrospective study included 533 consecutive patients hospitalized for TA from January 2009 to April 2018. Anemia was diagnosed on the basis of hemoglobin level, according to World Health Organization criteria. **Results** A total of 194 patients (36.4%) were diagnosed with anemia. Most had mild anemia (177, 91.2%). Female patients were predominant (92.8% of anemic patients). Normocytic anemia (62.9%) was the most common pattern. Anemic patients were more likely than non-anemic patients to have dizziness (29.4% *vs.* 21.2%), low body mass index (22.0 ± 3.6 *vs.* 22.9 ± 3.4 kg/m^2), and active disease stage (64.9% *vs.* 50.1%); pulmonary involvement (12.4% *vs.* 26.8%), pulmonary hypertension (12.9% *vs.* 20.1%) and pulmonary hypertensive-target drugs (2.8% *vs.* 11.6%) were less common among anemic than non-anemic patients (all $P < 0.05$). Larger left ventricular end-diastolic diameter and lower left ventricular ejection fraction were observed in anemic patients. Over a median follow-up of four months, the increase of hemoglobin in anemic patients was associated with the use of iron supplementation. **Conclusions** Anemia is a very common concurrent condition in TA, especially in young, female patients. Patients with anemia are more likely to be in the active disease stage. Iron supplementation helps increase hemoglobin.

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Keywords: Anemia; Disease activity; Oral iron supplementation; Takayasu arteritis

1 Introduction

Takayasu arteritis (TA) is a type of large-vessel vasculitis that generally affects the aorta and its main branches. Pulmonary artery can also be involved. The active stage of TA arises most commonly in young females of reproductive age.

Anemia is a common condition with a wide variety of causes, including long-term infection, malnutrition, solid or hematological malignancies, and connective tissue disorders. Anemia has a higher prevalence among preschool children, young females, and elderly individuals than among others. According to the 2004 statistics of the Ministry of Health of the People's Republic of China, the overall prevalence of anemia in the Chinese population was 15.2%. Because anemia is common in the general population, anemia is often recognized as a comorbidity rather than a complication in TA patients. There is limited information from a large population on the influence of anemia on TA, although several studies have reported anemic TA patients with severe inflammation and poor general condition.[1,2] Studies in other populations have showed that anemia is linked to adverse outcomes. Anemia is associated with the mortality in patients with left ventricular dysfunction.[3] Anemia is a risk factor for cardiovascular disease outcomes in a community cohort aged from 45 to 64 years.[4] In TA, anemia is also linked with a history of cardiovascular diseases.[5] In rheumatoid arthritis (RA), anemia is linked with active disease stage, and control of inflammation improves anemia.[6]

In this retrospective study, we investigated the prevalence, clinical characteristics, and treatment of anemia in a large population of TA patients in China.

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2 Methods

This study protocol was approved by the Institutional Ethics Committee of Fuwai Hospital. Because of the retrospective design of this study, written informed consent was waived.

We retrospectively reviewed the medical records of 533 TA patients admitted to our hospital from January 2009 to April 2018. All patients fulfilled the criteria for TA established by the American College of Rheumatology.[7] Angiographic classification was made according to the Hata and Numano criteria.[8] Disease activity was determined according to the criteria of the National Institutes of Health.[9] Patients with a history of thalassemia or gastrointestinal tract bleeding were excluded.

Clinical characteristics, including demographic information (sex, age at first hospitalization), clinical course (symptoms, signs, age at symptom onset, disease duration), comorbid diseases (hypertension, dyslipidemia, diabetes mellitus, stroke, renal dysfunction), and medical therapy (prednisone, aspirin, statins, anti-hypertension drugs, iron supplementation), were extracted from the electronic medical records.

Prednisone is the fundamental anti-inflammatory drug in our expertise. The initial dose of prednisone is related to body weight; 0.5–1.0 mg/kg daily was used.

The following laboratory parameters were measured with the same type of machines using fasting venous blood samples: white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean cell hemoglobin (MCH), MCH concentration (MCHC), standard deviation in red blood cell distribution width (RDW-SD), platelet, mean platelet volume (MPV), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, and N-terminal brain natriuretic propeptide (NT-proBNP).

Anemia was diagnosed on the basis of hemoglobin level (< 130 g/L in men and < 120 g/L in non-pregnant women), according to World Health Organization cutoff points.[10] Mild anemia was defined for both sexes as hemoglobin ≥ 90 g/L and below the cutoff, moderate anemia as hemoglobin ≥ 60 and < 90 g/L, and severe anemia as hemoglobin < 60 g/L. CRP was considered elevated at levels > 8 mg/L. Elevated ESR was defined as > 20 mm/h in females and > 15 mm/h in males. Fecal occult blood test was referred to determine gastrointestinal bleed. In the follow-up period, the first recheck of blood indices after discharge was recorded.

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography. Pulmonary hypertension was defined if the pulmonary artery systolic pressure was above 35 mmHg.[11]

Fifty-eight patients underwent [18F]-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-PET/CT). Patients were defined as PET-active if the maximum standardized uptake value (SUV) of region of interest is higher than average liver uptake.

Statistical analysis was performed with SPSS 19.0. Continuous variables were presented as mean ± SD or median (Q1-Q3) and were compared with independent *t*-test or the Mann–Whitney *U* test. Categorical variables were presented as number (percentage) and were compared with the chi-square test or Fisher's exact test. Multivariable linear regression model was used to assess the association between change of hemoglobin and the use of iron supplementation at discharge. Age and sex were forced in the model. Other factors (iron supplements, prednisone, elevated ESR) with a P value < 0.2 in univariate analysis were entered into the model. A two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 General clinical features

The clinical features of patients with and without anemia are listed in Table 1. A total of 194 patients (36.4%) were classified as anemic. Female patients were predominant (92.8%) in the anemic group. The anemic patients had a short duration from symptom onset to assessment. Anemic patients had a lower BMI (22.0 ± 3.6 kg/m^2) than non-anemic patients. Dizziness, which was the most common chief complaint (29.4% of patients), was experienced more commonly among patients with anemia (P = 0.035). Blood pressure discrepancy between arms (71.6%) were more prevalent among patients with anemia. Type V arteritis was most common (40.8% of patients), followed by type I (30.9%). Pulmonary artery involvement was less prevalent among anemic than non-anemic patients. A higher percentage of anemic patients (64.9%) than non-anemic patients (50.1%) were in the active stage according to the criteria of the National Institutes of Health (P = 0.001). Patients with anemia were more likely to have an active result of 18F-PET/CT (80.0% *vs*. 52.6%, P = 0.041).

3.2 Anemia pattern and severity

A total of 177 (91.2%) had mild anemia and 17 (8.8%) had moderate anemia. None of the patients presented with severe anemia. Normocytic anemia was most common (122 patients, 62.9% of anemic patients), followed by hypochromic,

Table 1. Demographic information and clinical features of the patients with Takayasu arteritis.

	Anemia, *n* =194	Non-anemia, *n* = 339	*P* value
Female	180 (92.8%)	266 (78.5%)	< 0.001*
Age at enrollment, yrs	35.9 ± 13.7	37.7 ± 13.0	0.139
Under 30 yrs	78 (40.2%)	101 (29.8%)	0.014*
Age at symptom onset, yrs	26.3 ± 10.4	27.2 ± 10.2	0.377
Duration of clinical course, median (Q1-Q3), months	54.8 (18.0–159.0)	79.4 (24.1–189.1)	0.039*
Body mass index, kg/m^2	22.0 ± 3.6	22.9 ± 3.4	0.021*
BMI < 18.5 kg/m^2	26 (13.4%)	33 (9.7%)	0.194
Systolic BP, mmHg	132.0 ± 34.6	124.6 ± 31.7	0.014*
Diastolic BP, mmHg	71.8 ± 19.7	65.6 ± 18.4	< 0.001*
Angiographic type (*n* = 529)			0.361
I	59 (30.9%)	80 (25.2%)	
IIa	11 (5.8%)	18 (5.7%)	
IIb	13 (6.8%)	20 (6.3%)	
III	18 (9.4%)	44 (13.8%)	
IV	12 (6.3%)	32 (10.1%)	
V	78 (40.8%)	124 (39.0%)	
Coronary artery	12 (6.2%)	20 (5.9%)	0.894
Pulmonary artery	24 (12.4%)	91 (26.8%)	< 0.001*
Symptoms and signs			
Constitutional symptoms	20 (10.3%)	25 (7.4%)	0.241
Neurological			
Dizziness	57 (29.4%)	72 (21.2%)	0.035*
Headache	19 (9.8%)	26 (7.7%)	0.396
Syncope	11 (5.7%)	14 (4.1%)	0.418
Amaurosis	8 (4.1%)	10 (2.9%)	0.470
Visual disorders	14 (7.2%)	20 (5.9%)	0.549
Limbs			
BP discrepancies between arms	139 (71.6%)	207 (61.1%)	0.014*
Easy fatigability	22 (11.3%)	42 (12.4%)	0.720
Claudication	13 (6.7%)	23 (6.8%)	0.970
Cardiac			
Exertional dyspnea	27 (13.9%)	79 (23.3%)	0.009*
Chest tightness	43 (22.2%)	78 (23.0%)	0.823
Chest pain	15 (7.7%)	21 (6.2%)	0.496
Palpitation	16 (8.2%)	19 (5.6%)	0.236
Comorbid diseases			
Hypertension	105 (54.1%)	195 (57.5%)	0.447
Dyslipidemia	36 (18.6%)	68 (20.1%)	0.674
Diabetes mellitus	6 (3.1%)	8 (2.4%)	0.611
Angina	18 (9.3%)	35 (10.3%)	0.698
Stroke	12 (6.2%)	28 (8.3%)	0.382
Renal dysfunction	18 (9.3%)	20 (5.9%)	0.145
[#]NIH active	126 (64.9%)	170 (50.1%)	0.001*
[&]PET active	16 (80.0%)	20 (52.6%)	0.041*
Prednisone	146 (75.3%)	249 (73.5%)	0.647
Daily prednisone dose, mg	25.5 ± 8.4	23.5 ± 8.2	0.026*

Data are presented as mean ± SD or *n* (%) unless otherwise specified. *P < 0.05; [#]NIH active: patients in active disease stage according to the criteria of the National Institutes of Health; [&]PET active: number of patients with results of 18F-PET/CT and the percentage of patients with an active result. BMI: body mass index; BP: blood pressure.

Table 2. Laboratory findings in TA patients according to presence of anemia.

Variables	Anemia	Non-anemia	*P* value
ESR, mm/h	19 (9−38)	8.00 (4.00−16.00)	< 0.001*
CRP, mg/L	4.02 (1.87−11.92)	3.56 (2.05−9.53)	0.954
NT-proBNP, pg/mL	576.4 (287.4−1187.2)	490.6 (91.4−819.7)	0.001*
BUN, mmol/L	5.01 (4.11−6.41)	4.97 (3.97−6.10)	0.918
CREA, μmol/L	61.0 (52.4−71.4)	64.6 (54.0−75.0)	< 0.001*
WBC, 10^9/L	7.12 (5.89−8.52)	7.08 (5.89−8.71)	0.665
RBC, 10^{12}/L	4.11 (3.83−4.44)	4.64 (4.37−5.04)	< 0.001*
Hemoglobin, g/L	111 (102−117)	136 (127−147)	< 0.001*
HCT, L/L	0.342 (0.320−0.360)	0.410 (0.386−0.437)	< 0.001*
MCV, fL	83.7 (77.7−89.9)	88.5 (84.7−91.6)	< 0.001*
MCH, pg	26.7 (24.1−29.3)	29.6 (28.2−30.7)	< 0.001*
MCHC, g/L	319.0 (309.0−328.3)	333.0 (324.0−342.0)	< 0.001*
RDW-SD, fL	44.0 (40.2−47.2)	41.8 (39.8−45.0)	< 0.001*
RDW-CV, %	14.6 (13.2−16.3)	13.1 (12.5−14.0)	< 0.001*
Platelet, 10^9 g/L	258 (208−332)	227 (192−277)	< 0.001*
MPV, fl	10.1 (9.5−11.0)	10.5 (9.9−11.3)	< 0.001*

Values are median (Q1−Q3); *P < 0.05. BUN: blood urea nitrogen; CREA: creatinine; CRP: C-reaction protein; ESR: erythrocyte sedimentation rate; HCT: hematocrit; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; MPV: mean platelet volume; NT-proBNP: N-terminal brain natriuretic propeptide; RBC: red blood cell count; RDW-CV: coefficient variation of red blood cell distribution width; RDW-SD: standard deviation in red blood cell distribution width; WBC: white blood cell count; TA: Takayasu arteritis.

microcytic anemia (51 patients, 26.3%) and normochromic, microcytic anemia (19 patients, 9.8%). Megaloblastic anemia was seen in only two patients (1.0%). Among patients with moderate anemia, 82.6% had hypochromic, microcytic anemia and 17.6% had normocytic anemia.

3.3 Laboratory findings

The level of ESR and BNP was higher in anemic patients than in non-anemic patients. Variables related to erythrocyte measurements, including decreased RBC, Hemoglobin, hematocrit, MCV, MCH, MCHC and increased RDW-SD and MPV were observed in anemic patients (Table 2).

3.4 Echocardiography findings

Anemic patients had larger left ventricular end-diastolic diameter (48.3 ± 6.9 *vs*. 46.5 ± 8.1 mm, P < 0.05) and lower left ventricular ejection fraction (61.6% ± 10.5% *vs*. 64.2% ± 8.5%) than non-anemic patients. The ratio of mitral regurgitation was higher (25.3% *vs*. 13.0%). The frequency of pulmonary hypertension was lower (12.9% *vs*. 20.1%; Table 3).

3.5 Treatment and short-term follow-up

Compared with anemic patients, the use of pulmonary

Table 3. Echocardiography findings between patients with and without anemia.

Variable	Anemia	Non-anemia	*P* value
Aortic annulus, mm	21.0 ± 2.2	21.3 ± 2.6	0.253
Valsalva's sinus, mm	30.8 ± 6.3	30.8 ± 6.0	0.406
Ascending aorta, mm	30.3 ± 4.5	30.7 ± 4.8	0.938
LAD, mm	33.5 ± 6.4	32.6 ± 5.4	0.097
IVSD, mm	9.6 ± 2.3	9.6 ± 2.0	0.832
LVPWD, mm	9.3 ± 2.3	9.3 ± 1.8	0.703
LVEDD, mm	48.3 ± 6.9	46.5 ± 8.1	0.009*
LVEF, %	61.6 ± 10.5	64.2 ± 8.5	0.004*
Main pulmonary artery, mm	23.1 ± 5.4	23.7 ± 4.6	0.216
AR	64 (33.0%)	85 (25.1%)	0.050
MR	49 (25.3%)	44 (13.0%)	< 0.001*
TR	30 (15.5%)	58 (17.1%)	0.623
PR	8 (4.1%)	20 (5.9%)	0.377
PH	25 (12.9%)	68 (20.1%)	0.036*

Values are *n* (%) or mean ± SD. AR: aortic regurgitation; IVSD: interventricular septal thickness at diastole; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVPWD: left ventricular posterior wall thickness at diastole; MR: mitral regurgitation; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; PR: pulmonary regurgitation; TR: tricuspid regurgitation. PH was defined as PASP ≥ 35 mmHg.

hypertensive-target drugs was more common in non-anemic patients (11.6% *vs*. 2.8%, $P = 0.002$). The daily dose of prednisone was higher in anemic patients than in non-anemic patients (25.5 ± 8.4 *vs*. 23.5 ± 8.2 mg, $P = 0.026$). Aspirin (61.9% *vs*. 65.1%, $P = 0.455$), statins (26.7% *vs*. 28.0%, $P = 0.756$), and anti-hypertension medicine (55.7% *vs*. 47.2%, $P = 0.060$) were similar between anemic and non-anemic patients at discharge.

Oral iron supplementation therapy was prescribed in 35 anemic patients with a dose of elemental iron ranging from 20 to 120 mg/day.

After a median follow-up of 4.0 months (2.1–11.8 months), 110 anemic patients had a recheck of blood indices. In total, 43.7% (47/110) of anemic patients remained anemic, including 42.0% (34/81) of anemic patients without iron supplementation and 44.8% (13/29) of anemic patients with iron supplementation ($P = 0.790$). Hemoglobin increased more among patients with iron supplementation than among those without supplementation (20.1 ± 18.6 *vs*. 8.7 ± 15.9 g/L, $P = 0.005$). After adjusting for age, female gender, initiation of prednisone at discharge, and elevated ESR, multivariable linear analysis showed association between iron supplementation at discharge and increase of hemoglobin ($P < 0.008$) (Table 4).

4 Discussion

In this retrospective study, we found that anemia was common among TA patients (36.4%). Mild anemia and normocytic anemia was predominant. Anemic patients also had a lower body mass index and a higher prevalence of dizziness than non-anemic patients. Anemic patients were more common than non-anemic patients in the active stage of disease, according to National Institutes of Health criteria or the results of 18F-PET/CT. Echocardiography showed that anemic patients had larger left ventricle and lower left ventricular ejection fraction. It was also attractive that non-anemic patients were more likely to have pulmonary artery involvement, pulmonary hypertension and pulmonary hypertensive-target drugs. After adjusting for confounders, oral iron supplementation increased hemoglobin level.

The prevalence of anemia among TA patients is different; studies showed anemia with a prevalence of 62.9% (22/35) in children, 37.1% (13/35) in adolescents, and 35.3% (55/156) in adults,[12,13] which decreased with the increase of age.

In inflammatory disease, iron deficiency anemia (IDA) and anemia of chronic disease (ACD) are two main causes of anemia, and ACD is more common than IDA.[14] ACD might be more common in TA. In this study, normocytic anemia was up to 62.9%. Anemic patients were more likely to be in the active disease stage and changes in blood indices related to anemia also supported active disease stage in TA patients. In a cross-section study, Liu, *et al*.,[13] reported that increased RDW was in correlation with high-sensitivity-CRP. Peng, *et al*.[15] showed that MPV might indicate

Table 4. Independent predictors of increased hemoglobin by multivariate linear regression analysis.

Increase of hemoglobin	B	95% CI	SE	Beta	*P* value	*t*
Iron supplements	7.779	(2.07, 13.487)	2.87	0.273	0.008	2.71
Prednisone	0.451	(–7.889, 8.792)	4.194	0.012	0.915	0.108
Female	2.566	(–7.215, 12.347)	4.919	0.053	0.603	0.522
Elevated ESR	–5.944	(–12.682, 0.795)	3.389	–0.178	0.083	–1.754
Age	–0.197	(–0.401, 0.007)	0.103	–0.211	0.059	–1.916

Factors that reached a *P* value < 0.2 in univariate analysis were included in the multiple regression model. Age and sex were forced in the model. CI: confidence interval; SE: standard error of the regression coefficient.

active disease in TA patients because MPV was negatively associated with CRP and ESR; the level of MPV increased after anti-inflammation therapy. We also observed increased RDW and decreased MPV in anemic patients. We speculated IDA existed in our population due to the followings. A total of 26.3% of the anemic TA patients had hypochromic, microcytic anemia, which was a main type of IDA. Women at reproductive age are at risk of IDA in general population,[16] and young women took up a high part in anemic patients. A study showed that patients with iron deficiency had lower classical hematologic indices including MCV, hemoglobin and MCH.[17] In our practice, patients with lower level of hemoglobin and MCV were more likely to initiate iron supplementation. The initiation of iron supplementation at discharge was associated with increased hemoglobin. Our anemic patients had elevated RDW, which is a marker of iron deficiency.[18]

Anemia may have adverse effects on heart function. Hemodynamic compensation for anemia (increased output and increased heart rate) and non-hemodynamic compensation (increased erythropoietin and increased oxygen extraction, activated sympathetic and renin-angiotensin-aldosterone systems) may result in cardiac enlargement, left ventricle hypertrophy and mitral regurgitation.[19,20] Decreased ejection fraction or higher level of BNP was more frequent in anemic patients than in non-anemic patients. These changes may be related to the high ratio of cardiovascular diseases in anemic people.[5,21]

The present study showed that anemia was associated with less pulmonary artery involvement, less ratio of pulmonary hypertension and less use of pulmonary hypertensive-target drugs. This may be a compensation for hypoxia in TA patients with pulmonary artery disorders. Hypoxia may increase the level of erythropoiesis, which promotes the proliferation and differentiation of erythroid precursors, causing an elevation of red blood cell mass.[22] As we diagnosed anemia due to the WHO criteria, patients with pulmonary disorder were more likely to be in the non-anemic stage. However, studies have reported that patients with pulmonary hypertension have iron deficiency without anemia due to elevated hepcidin;[23] iron deficiency without anemia may cause dyspnea and decreased activity endurance.[24] In addition, chronic anemia, especially genetic anemia, can result in pulmonary hypertension by the effect of intravascular hemolysis, pulmonary thromboembolism and response to hypoxia caused by anemia.[25] However, the clinical feature of our anemic TA patients is different from that of the patients with genetic anemia. Most of our anemic TA patients had mild anemia, and the anemia could be corrected after proper anti-inflammation therapy and iron supplementation. We considered that anemia did not raise pulmonary hypertension in TA patients.

ESR is influenced by anemia. In the present study, the level of ESR was higher in anemic patients than in non-anemic patients, but the level of CRP was similar. Anemic patients were more likely to be in the active disease according to the criteria of the National Institutes of Health and the results of 18F-PET/CT. Active disease stage and anemia could both contribute to raised ESR. Physicians should interpret the clinical value of raised ESR carefully for individual TA patients.

Several limitations should be addressed. First, we did not assess the data related to indices of iron, folate and vitamin B12, which were not routinely checked in our patients, so the proportion of IDA in TA could not be determined. Second, we assessed the blood indices, ESR and CRP at only two time points, the effect of dynamic changes of these parameters were unknown. Third, only 110 anemic patients came back to our center for a recheck of blood indices. There might be bias, although the blood indices during hospitalization of anemic patients with and without a follow-up did not have significant differences (data not shown). With the large sample size of TA patients, this study offers an overview of anemia in TA patients.

In conclusion, anemia was common among TA patients and was more common in young, female patients. Anemic patients were more likely to be in the active disease stage. Anemia affects cardiac function. Oral iron supplementation helped increase hemoglobin.

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