

# Clinical comparisons of patients with giant cell arteritis with versus without fever at onset

Journal of International Medical Research

2019, Vol. 47(11) 5613–5622

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DOI: 10.1177/0300060519875379

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## Abstract

**Objective:** Giant cell arteritis (GCA) is the most common systemic vasculitis in individuals aged  $\geq 50$  years. Some patients with GCA who develop fever at onset without typical ischemic manifestations may be misdiagnosed with fever of unknown origin.

**Methods:** In the present study, we retrospectively evaluated the clinical records of patients with GCA. Patients with and without fever at onset were compared.

**Results:** This study included 91 patients with GCA, 55 of whom had fever at onset. The patients with fever at onset showed a lower frequency of jaw claudication and arthralgia and a higher percentage of constitutional symptoms than patients without fever. Additionally, their laboratory results revealed a lower percentage of positive anti-neutrophil cytoplasmic antibody. Furthermore, a lower proportion of affected intracranial vessels was found in patients with fever at onset. Finally, the proportion of biopsy-positive cases was higher in patients with than without fever at onset.

**Conclusions:** In this study, 60.4% of patients with GCA had fever at onset. Patients in this group usually had more severe inflammation with a potentially lower risk of ischemic accidents of the central nervous system than patients without fever at onset.

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## Keywords

Fever, giant cell arteritis, inflammation, ischemic manifestation, constitutional symptoms, systemic vasculitis

Date received: 13 March 2019; accepted: 20 August 2019

## Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis affecting medium and large vessels in individuals aged  $\geq 50$  years.<sup>1</sup> The clinical features of GCA are largely dependent upon the topography of the arteritis, which is often symmetric in paired arteries.<sup>2</sup> A diagnosis of GCA is usually suggested by the classic presentation with ischemic manifestations of cranial vessels and other great vessels, including the aorta and its branches. However, a variable proportion of patients also develop systemic symptoms such as fever, malaise, fatigue, and weight loss. Moreover, some patients are even diagnosed with fever of unknown origin.<sup>3</sup> Thus, diagnosis of GCA in patients with atypical clinical features is challenging. This requires clinicians to establish the proportion of patients with GCA who present with fever at onset. Clinicians must also elucidate the patients' clinical features, including the affected vessels, laboratory tests, and prognosis of GCA with or without fever at onset.

In the present study, we retrospectively analyzed a cohort of patients with GCA at Peking Union Medical College Hospital, Beijing, China to address the above-described issues.

## Materials and methods

### Patients

Patients who were preliminarily diagnosed with GCA at Peking Union Medical College Hospital, Beijing, China from November 1998

to October 2017 were enrolled. All patients fulfilled the 1990 American College of Rheumatology diagnostic criteria for GCA.<sup>4</sup> All patients were followed up for the evaluation of clinical outcomes.

### Clinical data collection

The patients' clinical characteristics, including signs and symptoms, laboratory findings, and angiographic findings at the time of diagnosis, were obtained from the medical records and retrospectively evaluated. Central nervous system (CNS) symptoms included vertigo, transient ischemic attack (TIA), and stroke, which were confirmed by neurologists. Comorbid diseases assessed in this study included arteriosclerosis, smoking, diabetes, coronary artery disease, cerebrovascular disease, hypertension, and dyslipidemia. Fever was defined as an axillary temperature of  $\geq 37.3^{\circ}\text{C}$ , while fever at onset was defined as fever as the first symptom.

The vascular evaluation involved a review of radiologic data obtained from digital subtraction angiography, ultrasonography, computed tomography angiography, magnetic resonance angiography, and positron emission tomography.

During follow-up, the patients' clinical signs, symptoms, and laboratory results were also evaluated. Patients who underwent therapy and showed gradual tapering of the disease severity without recurrence were considered stable. In contrast, patients who underwent therapy and showed tapering of the disease with recurrence of GCA or with comorbid infections were considered unstable.

### Statistical analysis

Continuous variables are presented as mean and standard deviation, and categorical variables are presented as absolute frequency and percentage. Patients with GCA were divided into two groups according to the onset of fever. The two groups were compared using Student's t-test for continuous variables. The chi-squared test was performed to compare categorical variables. All statistical tests were two-sided, and  $p$ -values of  $<0.05$  were considered statistically significant. All data analyses were conducted using SPSS 20.0 software (IBM Corp., Armonk, NY, USA).

### Ethical approval

This study was approved by the Ethics Board of Peking Union Medical College Hospital (ethics approval number S-K437), and informed consent was obtained from all patients.

## Results

**Patients.** In total, 117 patients were included in this study. After clarifying the diagnosis and excluding patients with an ambiguous diagnosis or obvious missing data, 91 patients were finally included in the study.

**Sociodemographic data of patients with GCA presenting with fever at onset.** The main clinical and laboratory features of patients with fever at onset are summarized in Tables 1 and 2. Of all 91 patients with GCA, 55 (60.4%) (28 women and 27 men) had fever at onset prior to other symptoms. A total of 36 patients did not report fever at onset, and 19 patients had delayed fever before the diagnosis of GCA.

**Clinical differences between patients with and without fever at onset.** The patients' clinical features are summarized in Table 1. Of all 91 patients, 50 (54.9%) were female (male:female ratio, 1.00:1.22).

The average age at the time of GCA diagnosis was about 65 years, and no difference was found between the two groups. No differences in age or sex were found between patients with and without fever. The duration from onset to diagnosis was also similar in both groups. The comorbid diseases were similar in both groups. Patients with fever exhibited a lower frequency of headache, scalp pain, visual loss, myalgia, and hearing impairment than the remaining patients with GCA, although the differences were not statistically significant. However, patients with GCA who had fever at onset demonstrated a lower frequency of jaw claudication ( $p=0.025$ ) and arthralgia ( $p=0.020$ ) than those without fever. Patients with fever had a significantly higher percentage of constitutional symptoms (including fatigue, night sweats, and anorexia) than those without fever ( $p=0.019$ ). Weight loss was more frequently reported in patients with than without fever, although the difference was not significant. Among the patients with fever at disease onset, four presented with TIA and five with stroke. Among the patients without fever, five and seven presented with TIA and stroke, respectively. No patients presented solely with vertigo. A lower proportion of CNS involvement (vertigo, TIA and stroke) was seen in patients with fever at disease onset, and this result was consistent with the lower rate of involvement of intracranial vessels in this group; however, the difference in CNS symptoms was not significant. There was no difference in the proportion of polymyalgia rheumatica between the two groups.

**Laboratory differences between patients with and without fever at onset.** Table 2 shows the laboratory results of the patients with GCA. Patients with fever at onset had a higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and platelet (PLT) count than patients without fever at onset; however, the differences did

**Table 1.** Clinical features and comorbid diseases of patients with GCA with and without fever at onset.

	GCA with fever n = 55	GCA without fever n = 36	p-value
<b>Sociodemographics</b>			
Age at diagnosis, years	65.13 ± 7.74	65.61 ± 7.65	0.770
Disease course, months	8.41 ± 18.36	9.28 ± 15.85	0.812
<b>Sex</b>			
Male	27 (49.1)	14 (38.9)	0.339
Female	28 (50.9)	22 (61.1)	
<b>Clinical signs and symptoms</b>			
Headache	35 (63.6)	29 (80.6)	0.084
Scalp tenderness or pain	12 (21.8)	12 (33.3)	0.223
Tenderness and abnormal pulsation of temporal artery	13 (23.6)	7 (19.4)	0.637
Visual loss	19 (34.5)	16 (44.4)	0.343
Myalgia	30 (54.5)	21 (58.3)	0.722
CNS symptoms	9 (16.4)	12 (33.3)	0.060
Hearing loss	13 (23.6)	10 (27.8)	0.657
Jaw claudication*	11 (20.0)	15 (41.7)	<b>0.025</b>
Arthralgia*	23 (41.8)	24 (66.7)	<b>0.020</b>
GI symptoms	8 (14.5)	4 (11.1)	0.636
Constitutional symptoms*	42 (76.4)	19 (52.8)	<b>0.019</b>
Weight loss	33 (60.0)	17 (47.2)	0.231
PMR	29 (52.7)	21 (58.3)	0.599
<b>Comorbid diseases</b>			
Atherosclerosis	18 (32.7)	15 (41.7)	0.386
Smoking	20 (36.4)	13 (36.1)	0.980
Diabetes	9 (16.4)	5 (13.9)	0.749
Cerebrovascular disease	5 (9.1)	3 (8.3)	0.901
Coronary artery disease	8 (14.5)	5 (13.9)	0.930
Hypertension	18 (32.7)	14 (38.9)	0.547
Dyslipidemia	20 (36.4)	11 (30.6)	0.568

Data are presented as mean ± standard deviation or n (%).

CNS symptoms: vertigo, transient ischemia attack, stroke; GI involvement: abdominal pain, abdominal distention;

Constitutional symptoms: fatigue, night sweats, anorexia.

CNS, central nervous system; GCA, giant cell arteritis; GI, gastrointestinal; PMR, polymyalgia rheumatica.

\*Statistically significant difference.

not achieve statistical significance. The two groups did not differ significantly in the white blood cell, lymphocyte, or monocyte count. The albumin level was significantly lower ( $p=0.014$ ) and the hemoglobin level was slightly lower in patients with fever. The percentage of positive anti-neutrophil cytoplasmic antibody (ANCA) was significantly lower in patients with than without fever ( $p=0.004$ ). Other laboratory results

including the levels of anti-nuclear antibody, anti-phospholipid antibody, lupus anticoagulant, anti-cardiolipin antibody, anti- $\beta_2$  glycoprotein 1 antibody, and immunoglobulin G, were similar between the two groups.

**Differences in vessel involvement and biopsy results between patients with and without fever at onset.** A total of 45 (49.5%) patients underwent temporal

**Table 2.** Laboratory findings of patients with GCA according to fever onset.

	GCA with fever		GCA without fever			p-value	
	Mean $\pm$ SD (range)	n (%)	Total n	Mean $\pm$ SD (range)	n (%)		Total n
ESR, mm/h	94.92 $\pm$ 27.54		55	85.00 $\pm$ 27.35		36	0.095
CRP, mg/L	87.58 $\pm$ 55.38		55	67.93 $\pm$ 70.86		36	0.165
ALB, g/L*	31.54 $\pm$ 3.94		54	34.14 $\pm$ 5.17		35	<b>0.014</b>
WBC, $\times 10^9$ /L	8.83 $\pm$ 3.99		54	9.46 $\pm$ 4.83		35	0.525
LYM, $\times 10^9$ /L	1.42 $\pm$ 0.70		54	1.57 $\pm$ 0.62		35	0.313
MONO, $\times 10^9$ /L	1.10 $\pm$ 1.31		54	0.99 $\pm$ 0.76		35	0.620
HGB, g/L	103.57 $\pm$ 17.26		54	112.09 $\pm$ 21.83		35	0.056
PLT, $\times 10^9$ /L	404.09 $\pm$ 149.33		54	342.06 $\pm$ 150.40		35	0.061
ANA positivity		9 (16.7)	54		9 (26.5)	34	0.267
ANCA positivity*		3 (6.0)	50		10 (29.4)	34	<b>0.004</b>
APS positive		6 (27.3)	22		4 (19.0)	21	0.523
Elevated IgG		11 (25.0)	44		10 (33.3)	30	0.435

\*Statistically significant difference.

ALB, albumin; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; APS, anti-phospholipid antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; HGB, hemoglobin; IgG, immunoglobulin G; LYM, lymphocyte; MONO, monocyte; PLT, platelet; SD, standard deviation; WBC, white blood cell.

**Table 3.** Artery distribution and biopsy results of patients with GCA according to fever onset.

	GCA with fever		GCA without fever		p-value
	n (%)	Total n	n (%)	Total n	
Intracranial*	14 (37.8)	37	20 (69.0)	29	<b>0.012</b>
Aortic arch and extracranial	34 (91.9)	37	24 (82.8)	29	0.259
Infra-aorta arch	26 (70.3)	37	18 (62.1)	29	0.483
Temporal	16 (34.0)	47	7 (20.6)	34	0.185
Biopsy-positive*	24 (92.3)	26	10 (52.6)	19	<b>0.002</b>

\*Statistically significant difference.

GCA, giant cell arteritis.

artery biopsy, and 34 (75.6%) showed histopathological changes typical of GCA. The intracranial vessels were less severely affected in patients with than without fever at onset ( $p=0.012$ ). Evaluation of the other arteries, including the extracranial arteries, temporal artery, aorta, and branches of the aorta, showed no significant differences between the two groups (Table 3).

**Difference in treatment between patients with and without fever at onset.** Glucocorticoids were used in all 91 patients,

and most of the patients were also treated by immunosuppressive drugs such as cyclophosphamide (CTX) and methotrexate (MTX). In Peking Union Medical College Hospital, CTX is more widely used than MTX in patients with vasculitis. Among the patients with GCA who had fever at onset in the present study, only seven (12.7%) were not treated with immunosuppressive drugs, and three were treated with immunosuppressive drugs other than CTX and MTX. Among the patients without fever at onset, four (11.1%) were not treated

with immunosuppressive drugs and three were treated with immunosuppressive drugs other than CTX and MTX. No significant differences were found in the proportions of glucocorticoid and immunosuppressive drug use.

#### Differences in follow-up results between patients with and without fever at onset.

The median follow-up period was 86.04 months (range, 3–218 months). During the follow-up, each group lost seven patients (Table 4). The patients were categorized into four subsets according to their symptoms: stable, unstable, comorbid with malignant tumors, and death. No significant differences were observed in each of the subsets between patients with and without fever at onset. However, one and four patients developed ischemic events among the patients with and without fever at onset, respectively. Among patients with fever at onset, one developed acute myocardial infarction; among patients without fever at onset, three developed acute myocardial infarction and one developed acute ischemic stroke.

## Discussion

The average age at the time of GCA onset is reportedly about 76.7 years,<sup>5</sup> which is higher than that of our patients. Additionally, previous research has demonstrated that women are two to three times more commonly affected<sup>6</sup>; in the present study, however, the proportion of female patients was about

50%. These differences in average age and sex between our study and others may be due to the small sample size of the present retrospective study, although our sample size is the largest in Chinese research to date. In this study, fever at onset was observed in 60.4% of the patients with GCA. This frequency seems to be consistent with that reported in previous case series. Liozon et al.<sup>7</sup> reported that 55% of 175 patients with biopsy-proven GCA had fever. Bengtsson and Malmvall<sup>8</sup> found that 64.2% (61/95) of patients with GCA reported morning temperatures ranging from 38.1°C to 39°C. However, Gonzalez-Gay et al.<sup>9</sup> reported that fever was observed in only 10% of the patients with biopsy-proven GCA, which is much lower than that observed in the current study. These differences among the studies might be attributed to the different definitions of fever and different samples selected from among patients with GCA. These results should be interpreted with caution because our definition of fever differs from that in previous reports; additionally, the present study focused on fever as the initial symptom.<sup>7–9</sup>

The relationship between fever and the risk of developing ischemic manifestations of GCA is controversial. Patients with strong inflammatory responses manifested by a high ESR, anemia, a low albumin level, and fever reportedly have a low risk of developing severe cranial ischemic complications.<sup>10</sup> Several other studies have partially supported the conclusion that low

**Table 4.** Follow-up results of GCA patients according to fever onset.

	GCA with fever		GCA without fever		p-value
	n (%)	Total n	n (%)	Total n	
Stable	24 (50.0)	48	13 (44.8)	29	0.659
Unstable	16 (33.3)	48	10 (34.5)	29	0.918
Comorbid with tumors	1 (2.1)	48	1 (3.4)	29	0.715
Death	7 (14.6)	48	5 (17.2)	29	0.755

GCA, giant cell arteritis.

inflammatory responses are associated with a high risk of developing irreversible cranial ischemic complications (ICIC).<sup>9,11</sup> However, another study did not demonstrate an association between the inflammatory response and the risk of developing ICIC. The current study confirmed that patients with fever at onset had a low risk of developing ischemic events, including CNS symptoms and jaw claudication; this partially supports the conclusions by Cid et al.<sup>10</sup>

The mechanisms underlying the robust inflammatory responses of patients with GCA exhibiting a low risk of ICIC remain unknown. These mechanisms could involve inflammation-induced angiogenic activity in patients with strong inflammatory responses that play a compensatory role in ischemic complications.<sup>12</sup>

Patients with GCA with fever at onset showed high levels of inflammatory markers, including the ESR, C-reactive protein level, platelet count, lower albumin, and anemia, as well as a high frequency of constitutional symptoms. Although some differences were not statistically significant, the results are compatible with the common clinical features of fever.

With respect to the vasculature pattern, GCA is characterized by subacute granulomatous inflammation of the aorta and its major branches with particular tropism for the extracranial carotid artery branches in patients >50 years of age.<sup>13</sup> The pattern of arterial involvement in 12 autopsy cases demonstrated that the presence of arterial segments showing significant elastic tissue in the media and external elastic lamina was correlated with increased artery involvement.<sup>14</sup> Therefore, the cerebrovascular ischemic events in patients with GCA have been reported to be caused by involvement of extradural vertebral and carotid arteries with high-grade stenosis or occlusions, wherein the elastic fibers are more abundant than those in the intracranial arteries.<sup>15</sup> Because of the limited sample

size in the present study, we were unable to evaluate subgroups of different intracranial arteries such as the anterior cerebral artery, middle cerebral artery, posterior cerebral artery, vertebral artery, and basilar artery.

About 3% to 4% of patients with GCA reportedly develop cerebrovascular ischemic events.<sup>16</sup> In the present study, 23.1% (21/91) of the patients with GCA showed CNS involvement, which is quite higher than that reported previously. This discrepancy could be attributed to the broad definition of CNS involvement, which included vertigo, TIA, and ischemic stroke from the onset of the disease to GCA diagnosis. Because of the limited sample size, we could not establish subgroups for these three symptoms. Another possibility is that some vessels' involvement was evaluated by ultrasound in addition to magnetic resonance angiography with contrast or positron emission tomography-computed tomography because it is difficult to differentiate vasculitis from atherosclerosis. The European League Against Rheumatism has recommended imaging techniques for diagnosis and evaluation of large vessel vasculitis in clinical practice, while the recommendation also demonstrated that biopsy could not be replaced by imaging tests because none of the techniques was 100% sensitive.<sup>17,18</sup> Another study demonstrated the importance of temporal artery biopsy as the standard test for most patients suspected to have GCA, although it lacked sensitivity.<sup>19</sup> Therefore, the evaluation and diagnosis of GCA contains comprehensive advice and is not limited to a certain imaging test or to temporal artery biopsy.

The present study also demonstrated a significantly lower percentage of intracranial vessel involvement in patients with fever at onset, which is in agreement with the low proportion of cranial ischemic complications. This result reconfirms the conclusion that patients with GCA who develop strong inflammatory responses may have a low risk of ischemic events.<sup>10</sup> Other evaluations

of the vessels did not demonstrate a significant difference between the groups because of the small sample size. Hence, a large prospective study is required to evaluate the vessel distribution of GCA.

Another result that requires consideration is the significantly low percentage of ANCA positivity in patients with fever at onset. The association of ANCA with GCA remains obscure despite several published studies.<sup>20–23</sup> ANCA is speculated to play a key role in the pathogenesis in a specific group of patients with small- and medium-sized vessel vasculitis. Small vessel vasculitis (SVV) and vasa vasorum vasculitis partially constitute the histopathological spectrum of GCA.<sup>24,25</sup> Compared with classic GCA, patients with GCA characterized by SVV show several distinct clinical features including less frequent cranial manifestations, a less severe inflammatory response, and a high frequency of musculoskeletal manifestations.<sup>25</sup> In the present study, patients without fever at onset manifested less severe inflammatory responses and a high frequency of arthralgia, which might be due to the underlying SVV. However, the pathology of the temporal arteries in both groups of patients has not yet been reevaluated to confirm the hypothesis.

This study has several advantages. In China, the prevalence of GCA is often underestimated, and some physicians lack the experience necessary to diagnose GCA. To the best of our knowledge, this is the largest single-center study in the English language from mainland China. Additionally, this study addressed the novel aspect of fever at onset in patients with GCA, which is essential for clinicians.

Nevertheless, the current study has several limitations, including its retrospective design, small sample size, and incomplete dataset, which might have biased the findings. Therefore, caution is necessary when interpreting the results.

In conclusion, 60.4% of the patients with GCA in the present study had fever at

onset, and such patients usually had more severe inflammation and a lower risk of ischemic events involving the CNS than those without fever at onset. Clinicians should be aware of the clinical features of these patients and consider the diagnosis of GCA despite the absence of typical ischemic manifestations. The relationship between fever and the risk of ICIC remains unknown, and additional studies are essential to elucidate this relationship. The vascular distribution of GCA with fever at onset was not well demonstrated, and a large-sample study is imperative.

### **Acknowledgements and authors' contributions**

We thank all the physicians from the Department of General Internal Medicine of Peking Union Medical College Hospital who participated in the care of the patients in this study. YZ and DW drafted the manuscript and carried out the data analysis. YY collected the clinical data and followed up all the patients. HF and WZ participated in the study design. XZ is accountable for the conception and execution of the study. All authors read and approved the final manuscript.

### **Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

### **Funding**

This work was funded by the Basic Research Project of Peking Union Medical College (2018PT310017).

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