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## Utility of Erythrocyte Sedimentation Rate and C-Reactive Protein for the Diagnosis of Giant Cell Arteritis

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### Abstract

**Objectives—**1) To evaluate the utility of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for the diagnosis of giant cell arteritis (GCA) 2) to determine the frequency of normal ESR and CRP at diagnosis of GCA.

**Methods—**All patients undergoing temporal artery biopsy (TAB) between 2000 and 2008 were identified. Only subjects with both ESR and CRP at the time of TAB were included. The medical records of all patients were reviewed.

**Results—**We included 764 patients (65% women), mean age 72.7 ( $\pm 9.27$ ) years, who underwent TAB. Biopsy was consistent with GCA in 177 patients (23%). Elevated CRP and elevated ESR provided a sensitivity of 86.9% and 84.1% respectively, for a positive TAB. The odds ratio (OR) of a concordantly elevated ESR and CRP for positive TAB was 3.06 (95% CI 2.03, 4.62) while the OR for concordantly normal ESR and CRP was 0.49 (95% CI 0.29, 0.83).

Seven patients (4%) with a positive TAB for GCA had a normal ESR and CRP at diagnosis. Compared to GCA patients with elevated markers of inflammation, a greater proportion of these patients had polymyalgia rheumatica symptoms ( $p=0.008$ ) while constitutional symptoms, anemia and thrombocytosis were observed less often ( $p<0.05$ ).

**Conclusions—**CRP is a more sensitive marker than ESR for a positive TAB that is diagnostic of GCA. There may be clinical utility in obtaining both tests in the evaluation of patients with suspected GCA. A small proportion of patients with GCA may have normal inflammatory markers at diagnosis.

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## INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous vasculitis involving the aorta and its primary and secondary branches (1). GCA is the most common form of systemic vasculitis in people over the age of 50 years, with an annual incidence of approximately 19 per 100,000 people aged 50 years and above (2). The lifetime risk for developing GCA is estimated at 1% for women and 0.5% for men (3). Vision loss due to ischemic optic neuropathy is a dreaded complication of GCA and therefore, prompt diagnosis and treatment are essential (1).

To date, there is no specific blood biomarker for GCA and histologic examination of a temporal artery biopsy (TAB) specimen is considered the gold standard diagnostic test. Laboratory findings in GCA are non-specific but most patients have elevated acute phase reactants at disease onset. An elevated erythrocyte sedimentation rate (ESR) has been considered a hallmark of this disease and is one of the ACR classification criteria for GCA (4). The C-reactive protein (CRP) is an acute phase reactant synthesized in the liver and is a sensitive marker of systemic inflammation. While CRP is often used in conjunction with the ESR for the initial evaluation of patients with suspected GCA, few studies have evaluated CRP performance in subjects undergoing TAB (5, 6).

We sought to evaluate the performance of ESR, CRP and a combination of the two tests for the diagnosis of GCA among all patients undergoing TAB. Secondly, we sought to evaluate the frequency of normal ESR and CRP at the time of GCA diagnosis in patients with a positive TAB, and describe the clinical characteristics of these patients.

## PATIENTS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board. Using the Mayo Clinic database, a data retrieval specialist identified all patients who underwent TAB at our institution between January 1, 2000 and December 31, 2008.

### Data collection

The medical records of all patients who underwent TAB were reviewed. Data regarding demographic information, date of biopsy and laboratory findings, including complete blood count (CBC), ESR and CRP prior to the biopsy were abstracted from the medical records. Pathology reports from all subjects undergoing TAB were reviewed to identify patients in whom TAB was interpreted as showing changes consistent with GCA. Patients with a positive TAB were all treated for GCA. In the subset of patients with biopsy-positive GCA, we also abstracted the date of first symptom onset, date of diagnosis of GCA, symptoms at disease onset, glucocorticoid use at the time of laboratory testing (if applicable) and use of non-steroidal anti-inflammatory medications at the time of laboratory testing.

ESR was measured by Westergren method. Based on Mayo Clinic clinical laboratory reporting, an ESR value of  $\leq 22$  mm/hour in men or  $\leq 29$  mm/hour in women was considered normal regardless of age. A normal CRP was defined as a value of  $\leq 8$  mg/L in all patients regardless of age.

### Exclusions

Subjects who did not have both ESR and CRP testing available in the 6 weeks prior to TAB.

### Statistical analysis

Descriptive statistics were used to summarize data. For the first portion of the study, sensitivity, specificity, positive and negative predictive value of ESR, CRP and the

combination of the two for a positive TAB were calculated. Logistic regression was used to evaluate the association between the acute phase reactants and positive TAB. Receiver operator characteristic (ROC) curves were used to determine the optimal cutoff value for CRP.

In the second portion of the study, we compared the clinical features of patients with GCA confirmed by TAB who had normal ESR and CRP to those of patients with elevated markers at the time of diagnosis. We used Fisher's exact test to compare categorical variables between patients with normal ESR and CRP at the time of diagnosis to patients with either test elevated. Rank sum tests were used to compare continuous variables between the two groups.

## RESULTS

A total of 1,106 subjects underwent 1,174 TAB at our institution between January 1, 2000 and December 31, 2008. TAB findings were consistent with GCA in 242 patients (21.9%).

### Performance of ESR and CRP among patients undergoing TAB

Of the 1,106 patients who underwent TAB, 764 (69.1%) had both ESR and CRP testing within 6 weeks before TAB and were included for this portion of the study. The study cohort therefore included 587 patients (77%) with a negative TAB and 177 patients (23%) with a positive TAB for GCA. Of the 177 patients with positive TAB, 165 patients (93.2%) met 1990 ACR Classification criteria for GCA. Twelve patients with positive TAB who did not meet 1990 ACR classification criteria included 8 patients with other cranial symptoms suspicious for GCA and 4 patients with symptoms of limb claudication and evidence of large-artery stenosis. We compared baseline demographics and the distribution of ESR and CRP in patients with a positive TAB for GCA to those with a negative TAB (Table 1). At baseline, patients with a positive TAB for GCA were on average, 2.4 years older than patients who had a negative TAB. The median ESR and CRP were also significantly higher in patients with a positive TAB compared to those with a negative biopsy. Additionally, a significantly greater proportion of patients with a positive TAB had a concordantly elevated ESR and CRP (81%) compared to subjects with a negative biopsy (59%).

The sensitivity, specificity, positive and negative predictive values of ESR, CRP and a combination of the two for a positive biopsy result are provided in Table 2. An elevated CRP provided a slightly higher sensitivity for a positive biopsy than an elevated ESR. The specificity of the ESR and CRP individually was low while the combination of elevated ESR and CRP provided modest specificity (41%). Both a normal ESR and normal CRP had excellent negative predictive values, with the CRP slightly outperforming the ESR. An elevated ESR was associated with increased odds ratio (OR) for a positive TAB (OR 2.22; 95%CI 1.43, 3.46) as was elevated CRP (OR 2.94; 95%CI 1.83, 4.71). The highest odds ratio for positive TAB was observed in subjects who had an elevation of both ESR and CRP (OR 3.06; 95% CI 2.03, 4.62). Conversely, if ESR and CRP were both normal the odds ratio for positive biopsy was reduced; OR 0.49 (95% CI 0.29, 0.83).

We performed a sensitivity analysis in which we included all subjects with TAB who had either ESR or CRP tested. The results of this analysis for ESR or CRP were similar to that reported in Table 2. When all subjects who had an ESR performed were included, elevated ESR had a sensitivity of 86% (193/225), specificity of 27% (217/810), positive predictive value of 25% (193/786) and negative predictive value of 87% (217/249). For CRP, the sensitivity of elevated CRP was 87% (155/178), specificity was 31% (183/599), positive predictive value was 27% (155/571) and negative predictive value was 89% (183/206). Based on estimates derived by modeling an ROC curve and including all subjects who

underwent TAB and had CRP testing performed, the optimal cut-off value for CRP was 26.9 mg/L, yielding a sensitivity of 75% and specificity of 51% (Figure 1a). Similarly, estimates derived by modeling an ROC curve for all subjects with TAB and ESR testing, the optimal cut-off value for ESR was 53 (Figure 1b).

Based on estimates derived by modeling an ROC curve, the optimal cut-off value for CRP was 26.9 mg/L, yielding a sensitivity of 75% and specificity of 51% (Figure 1a). Similarly, estimates derived by modeling an ROC curve for all subjects with TAB and ESR testing, the optimal cut-off value for ESR was 53 mm/hour which gave a sensitivity of 66% and specificity of 55% (Figure 1b).

### Normal ESR and CRP at diagnosis in GCA

The subset of 177 patients with GCA was used to evaluate the clinical characteristics of patients who had normal ESR and CRP at diagnosis. This included 130 women (73.4%) and 47 men (26.6%) with a mean age at diagnosis of 74.5 ( $\pm 7.8$ ) years. Table 3 summarizes the symptoms at diagnosis in all 177 patients.

The ESR and/or CRP were elevated in 159 (89.8%) patients while 18 patients (10.2%) had a normal ESR and CRP at the time of diagnosis. There was good concordance between ESR and CRP, as both were either elevated or normal in 163 patients (92.1%). However, 14 patients (7.9%) had discordant results; of these, CRP was elevated with a normal ESR in 9 patients.

Eleven of the 18 subjects with normal ESR and CRP were on glucocorticoids at the time of testing. Therefore, 7 (4%) patients had a normal ESR and CRP even in the absence of glucocorticoid use. Median ESR for these 7 patients was 13 mm/hour (range 3–25) with median CRP 4.4 mg/L (range 1.3–8.0 mg/L). While not statistically significant, the 7 patients with normal ESR and CRP tended to be younger, have a longer duration of symptoms and had fewer constitutional symptoms than the patients with elevated ESR and/or CRP (Table 4). Of concern, visual symptoms were present in 3 of the 7 patients (43%) with vision loss occurring in 1 patient (14.3%). A greater proportion of patients with normal ESR and CRP at the time of diagnosis had symptoms of polymyalgia rheumatica (Table 4). These patients also had a significantly lower platelet count and higher hemoglobin at the time of diagnosis compared to patients with an elevated ESR or CRP (Table 4).

## DISCUSSION

Biomarkers of inflammation, particularly the ESR and CRP, are often used in the evaluation of patients suspected of having GCA. However, performance of both in the diagnosis of GCA is not well described (5, 6). To our knowledge, the current study is the largest to date that evaluates these markers of inflammation in a cohort of patients undergoing TAB for diagnosis of GCA. Additionally, we also assessed the frequency and clinical characteristics of patients with biopsy-positive GCA who had normal ESR and CRP.

Only two prior studies have evaluated the usefulness of CRP in the diagnosis of GCA among subjects undergoing TAB (5, 6). In a study evaluating the sensitivity and specificity of different laboratory markers for the diagnosis of GCA, CRP ( $>0.5$  mg/dL) was more sensitive (sensitivity 100%) than ESR (sensitivity 97%) and the combination of the two provided the best specificity (97%) (6). However, the authors compared the test characteristics among patients with GCA to controls who were subjects seen in an ophthalmology practice for other conditions (6). Therefore, this study did not provide information on the performance of inflammatory markers in the setting of all-comers undergoing a TAB for suspected GCA. A more recent study evaluated the performance of

ESR and CRP among subjects undergoing a TAB and also concluded that elevated CRP was a better predictor of a positive biopsy than ESR (5). However, while the latter study included 3,001 subjects undergoing TAB (459 with positive biopsy), the frequency of CRP testing was low and only available in 20% of the patients (98 patients with GCA and 493 subjects with a negative biopsy). In our study, 66% of patients who underwent TAB had both ESR and CRP measured at the time of the procedure.

We were able to evaluate the test characteristics of ESR or CRP alone and the combination of the two to determine which performed better and whether there is clinical utility to testing both. As in previous reports, we found that elevated CRP had a higher sensitivity than ESR for GCA (86.4%). However, the specificity of either ESR or CRP alone was low (approximately 30%). This improved modestly to 41% when a combination of ESR and CRP were used. While the combination of ESR and CRP did not improve sensitivity, the highest odds ratio for a positive TAB and the diagnosis of GCA was observed when both ESR and CRP were concordantly elevated. Conversely, the combination of normal ESR and CRP was associated with decreased odds of having a positive TAB.

While the majority of patients with GCA have elevated markers of inflammation at clinical presentation, normal ESR or CRP has been reported in a small proportion of patients at diagnosis. The frequency varies between 4–14% depending on the study and the definition of normal values (7–9). In one study, 22.5% subjects with polymyalgia rheumatica or GCA had a normal ESR at diagnosis (10). In a population-based study of newly diagnosed GCA, 5.3% of 167 patients had an ESR less than 40 mm/hour (7). A meta-analysis evaluating the diagnostic value of clinical findings among patients suspected of having GCA estimated that about 4% patients with GCA present with normal ESR (9). Few studies have evaluated normal CRP at diagnosis, with estimates ranging from 2% to 14% (8, 11–13). In one study of 119 patients with GCA, only 3 subjects (1.7%) had a normal CRP at the time of GCA diagnosis, of whom 1 subject (0.8%) had a normal ESR and CRP (8). Other studies which have evaluated CRP at diagnosis have included subjects with PMR and/or GCA, reporting a prevalence of normal CRP to be between 1.2% and 20% (11–13). However, since these studies also included patients with PMR, it is difficult to draw conclusions regarding the subset of patients with GCA.

In our study, the prevalence of normal ESR and CRP in the absence of glucocorticoid use was 4%. We used cut-off values defined by our laboratory for the normal ranges of these tests in our analysis, rather than other possible, generally higher, values for ESR and CRP. All of the patients with normal inflammatory markers underwent TAB because of clinical symptoms suggesting GCA.

Compared to patients with elevated acute phase reactants and biopsy-confirmed GCA, the patients with normal markers had fewer constitutional symptoms. Additionally, other laboratory abnormalities including anemia and thrombocytosis were also less prevalent in those with normal ESR/CRP, suggesting an overall muted inflammatory response. This finding is similar to what has been reported in a population-based study evaluating low ESR (<40 mm/hour) at diagnosis (7). In that study, patients with a low ESR had fewer systemic symptoms (11%) than patients with GCA and elevated ESR (57%),  $p=0.02$  (7). Results from another study revealed a trend toward less anemia and less fever in patients with GCA who had an ESR of <50 mm/hour compared to those with elevated ESR (14). While not statistically significant, we found that the duration of symptoms antecedent to TAB and diagnosis of GCA was longer in patients with normal ESR and CRP compared to patients with elevated acute phase reactants. This likely reflects a delay in diagnosis in these patients with atypical findings. Of concern is that vision loss (transient or permanent) occurred in 3 of 7 patients with normal acute phase reactants. Previous studies have shown that a strong



inflammatory response may be protective against cranial ischemic complications including vision loss, possibly because of increased alertness to the potential for visual loss in these patients on the part of the managing physician (15). It is important to recognize that in the presence of clinical symptoms or findings of ischemic eye disease, GCA should be considered even in the absence of elevated markers of inflammation.

While our study includes a large cohort of subjects, several limitations need to be considered. This study was conducted at a tertiary care referral center. We only included cases with biopsy-positive GCA and therefore these results may not be applicable to all patients with GCA. There may also have been patients with clinically diagnosed GCA who had a negative TAB and were therefore misclassified. Given our research question of interest, we only included patients with both ESR and CRP testing available at the time of diagnosis. Also, the estimates for sensitivity and specificity of ESR and CRP are only applicable to patients in whom a decision has been made to perform a TAB. Given the referral nature of our practice, the prevalence of normal ESR and CRP in GCA patients may be higher than would be expected in the general population. Additionally, there may be greater vigilance for GCA at our center, leading to TAB even in atypical cases where markers of inflammation are normal.

## CONCLUSIONS

In this study, CRP was a more sensitive marker than ESR for GCA among subjects undergoing TAB. The combination of elevated ESR and CRP provided better specificity than either test alone and was associated with greater odds of a positive TAB. Among GCA patients with a positive biopsy, normal ESR and CRP was observed in 4% of cases. These patients tended to have an overall muted inflammatory response but more frequently had PMR symptoms. Our findings highlight that absence of a systemic inflammatory response as reflected in the currently routinely used ESR and CRP does not exclude GCA. TAB should be pursued in all patients where clinical suspicion of GCA is high. While ESR and CRP are often helpful for the diagnosis of GCA, they are nonspecific and better diagnostic markers are needed.

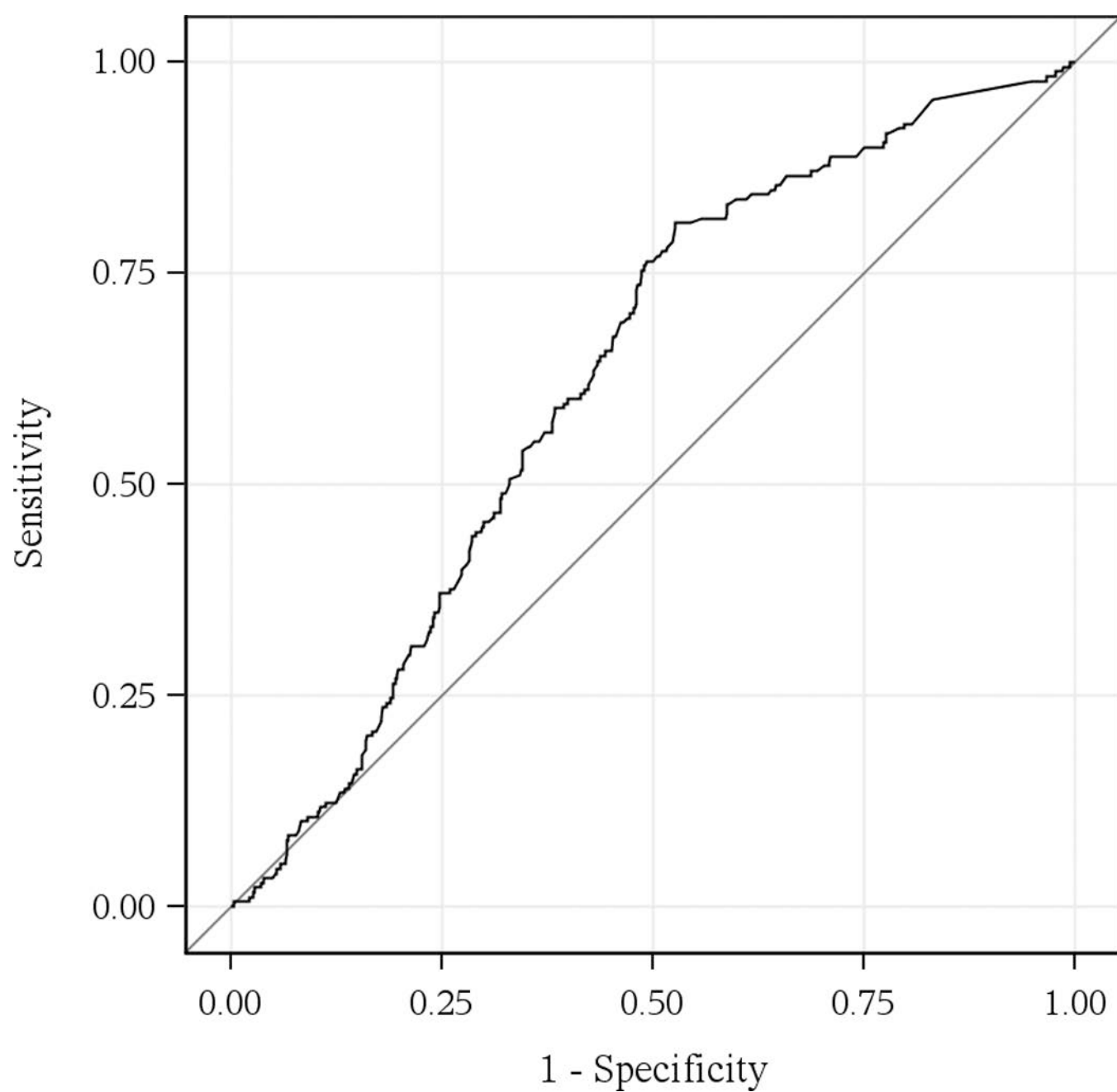
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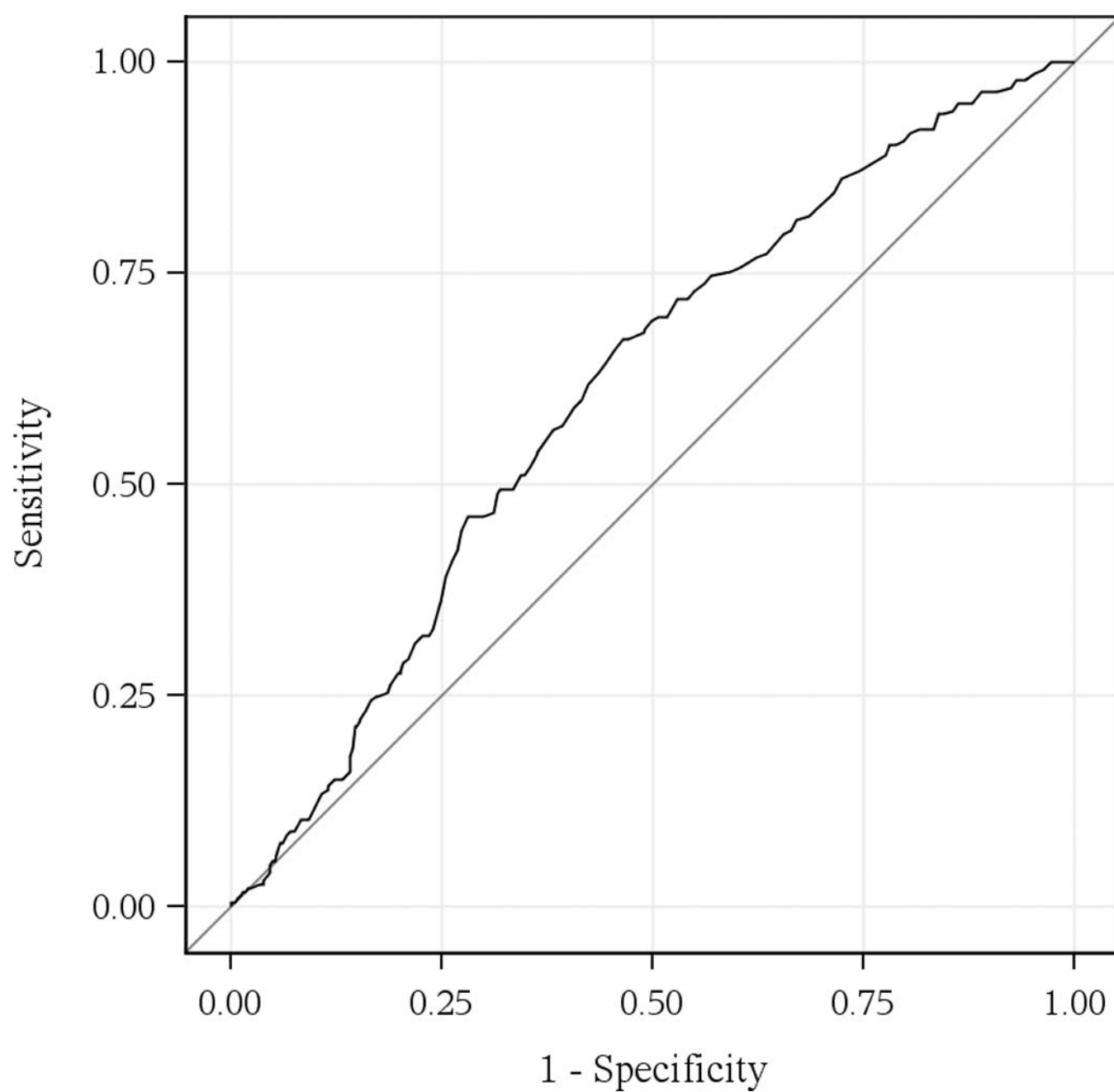
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**Figure 1.**  
Receiver operator characteristic curve of CRP (panel a) and ESR (panel b) in subjects undergoing temporal artery biopsy.

**Table 1**

Baseline and laboratory characteristics among 764 subjects undergoing a temporal artery biopsy (TAB)

Variable	TAB negative (N=587)	TAB positive (N=177)	p-value
Mean Age ( $\pm$ SD), years	72.1 (9.6)	74.5 (7.8)	0.008
Female Sex, No. (%)	371 (63.2)	130(73.4)	0.012
Median ESR (IQR), mm/hour	44.0 (25, 75)	62.0 (36, 91)	<0.001
Median CRP (IQR), mg/L	24.0 (6, 73)	52.0 (27, 95)	<0.001
ESR elevated, No. (%)	414(70.5)	149 (84.2)	<0.001
CRP elevated, No. (%)	408 (69.5)	153 (86.4)	<0.001
Elevated ESR and CRP, No. (%)	345 (58.8)	143 (80.8)	<0.001
Normal ESR and CRP, No. (%)	110(18.7)	18(10.2)	0.006

\* data presented as median with 25<sup>th</sup> and 75<sup>th</sup> percentile values

SD=standard deviation; No.=number; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; IQR=interquartile range

**Table 2**

Test characteristics of ESR, CRP and a combination of the two for positive temporal artery biopsy

	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>
ESR	84.2%	29.5%	26.4%	86.1%
	149/177	173/592	149/563	173/201
CRP	86.4%	30.5%	27.2%	88.6%
	153/177	179/587	153/561	179/202
ESR and CRP *	80.8%	41.2%	29.3%	87.7%
	143/177	242/587	143/488	242/276

\* evaluating subjects with both tests elevated

ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; PPV=positive predictive value; NPV=negative predictive value

**Table 3**

Symptoms at onset in 177 patients with GCA

Variable	No. (%)
Median duration symptoms (IQR), days	51.5 (18, 111.5)
Headache	111 (62.7)
Jaw claudication	78 (44.1)
Scalp sensitivity	65 (36.7)
Transient vision loss	37 (20.9)
Permanent vision loss	18 (10.2)
Subjective fever	39 (22.0)
Fatigue	62 (35.0)
Anorexia	21 (11.9)
Subjective weight loss	54 (30.5)
Polymyalgia rheumatica	54 (30.5)

GCA=giant cell arteritis; No.=number

**Table 4**

Clinical manifestations of GCA patients with normal ESR and CRP to those with elevated ESR and/or CRP

Clinical Variable	ESR and/or CRP elevated* N=138	ESR and CRP normal* N=7	p-value
Female gender, No. (%)	98 (71)	6 (85.7)	0.40
Age at diagnosis, Mean ( $\pm$ SD) years	74.5 (8.0)	70.0(5.9)	0.11
Symptom duration, Median (IQR) ** days	51(18, 101)	112(16, 167)	0.41
New headache, No. (%)	88 (63.8)	4(57.1)	0.72
Jaw claudication, No. (%)	65(47.1)	2 (28.6)	0.34
Scalp tenderness, No. (%)	50 (36.2)	2 (28.6)	0.68
Transient vision loss, No. (%)	30(21.7)	2 (28.6)	0.68
Permanent vision loss, No. (%)	13 (9.4)	1 (14.3)	0.67
Fever, No. (%)	33 (23.9)	0(0)	0.14
Fatigue, No. (%)	50 (36.2)	0(0)	0.05
Anorexia, No. (%)	17(12.3)	0(0)	0.32
Weight loss, No. (%)	43 (31.2)	1 (14.3)	0.34
Polymyalgia rheumatica, No. (%)	35 (25.4)	5(71.4)	0.008
Anemia, No. (%)	88 (68.8)	0(0)	<0.001
Hemoglobin, mean ( $\pm$ SD) g/dL	11.6(1.53)	13.4(0.99)	0.002
Thrombocytosis, No. (%)	46 (36.2)	0(0)	0.05
Platelet count, mean ( $\pm$ SD) $\times 10^9$ /L	424.2(135.2)	270.9(56.79)	0.001

\* Subjects on glucocorticoids were excluded

\*\* data presented as median with 25<sup>th</sup> and 75<sup>th</sup> percentile values

No=number; SD=standard deviation; IQR=interquartile ratio; NSAID=non-steroidal antiinflammatory drugs