Long-term Outcome for 120 Japanese Patients With Takayasu's Disease
Clinical and Statistical Analyses of Related Prognostic Factors

Kaichiro Ishikawa, MD; Shunzo Maetani, MD

Background Patients with Takayasu's disease, a chronic inflammatory arteriopathy of unknown cause, have variable clinical courses, and predictors of the long-term outcome are not well understood. We studied prognostic factors of this disease, based on follow-up results, and a new prognostic classification was proposed.

Methods and Results Life-table methods and Cox regression analyses were applied to clinical data on 120 patients who had been prospectively followed for a median of 13 years (range, 1 month to 34 years). The overall survival rate at 15 years after the diagnosis was 82.9% and remained the same for the remainder of the follow-up period. Univariate Cox analyses revealed that of the six dichotomous variables evaluated at diagnosis, four were statistically significant predictors, including complications (Takayasu's retinopathy, hypertension, aortic regurgitation, and aneurysm), pattern of the past clinical course, age of the patient, and calendar year of diagnosis. Thus, the 15-year survival was 66.3% versus 96.4% for patients with and without a major complication, 67.9% versus 92.9% for patients with and without a progressive course, 58.3% versus 92.7% for age >35 years and ≤35 years, and 79.9% versus 96.5% for patients diagnosed in 1957 through 1975 and in 1976 through 1990, respectively. The delay in diagnosis and the erythrocyte sedimentation rate (ESR) were of marginal significance. The multivariate Cox analysis showed that only two of the above variables were statistically independent predictors, ie, the major complication and the progressive course. In addition to these two factors, ESR was the third predictor, if the Cox stepwise elimination procedure was performed. These three predictors used in various combinations made a total of 1822 classifications theoretically feasible. Of these, a three-stage classification was selected as the best one, based on the Akaike information criterion. The presence of both major complication and progressive course (stage 3) was the worst prognostic indicator (43% survival at 15 years). In contrast, no patient died who had neither of these manifestations or who had a progressive course but an elevated ESR as well (stage 1).

Conclusions The long-term outcome for patients with Takayasu's disease seems best predicted by two major prognostic factors, ie, complications and the pattern of the past clinical course, as well as by ESR. Aggressive medical and surgical treatment may be considered for patients with a major complication and a progressive course (stage 3). (Circulation. 1994;90:1855-1860.)

Key Words • Takayasu's disease • arteriopathy • prognosis • survival

Takayasu's disease, a chronic inflammatory arteriopathy of unknown etiology, leads to both stenotic and ectatic changes, particularly occlusion.1 The common sites of involvement are the aorta and its main branches, and the pulmonary artery is often involved.2-4 Since there is a wide variation in the course,5-6 prediction of the outcome is difficult. Long-term follow-up and analysis of clinical signs and symptoms are important. In previous reports, we suggested that either the presence of a major complication (severe or multiple complications)3,6 or a progressive course (crescendo symptom patterns),7 particularly in combination,7 was an unfavorable prognostic indicator. This was confirmed by other investigators who also suggested other prognostic factors.8 However, we have found no documentation identifying independent predictors of outcome or the optimal combination of predictors, as based on multivariate analyses.

We have extended our previous studies to a larger series of patients who had been followed for a longer period of time, and we searched for independent prognostic factors. Also, an attempt was made to define a new prognostic classification using a computer-assisted exhaustive method.

Methods

Patients

During the 34-year period from May 1957 through December 1990, 130 consecutive Japanese patients with Takayasu's disease were seen at Kyoto University Hospital. For 120, the diagnosis was confirmed by angiography, autopsy, or both. The diagnostic work-up has been described in detail elsewhere.9 Of the 120, 111 were women and 9 were men, including a pair of twin sisters, two sisters, and a woman and her niece. Except for one patient, the detailed history taking and physical examinations were done exclusively by one of the authors in the vascular disease outpatient clinic or at the patient's bedside during admission. All past records and angiograms of the patients were reviewed.

Predictor Variables

Detailed definitions and categorization of the variables examined were reported elsewhere.3,6,7,10 All variables were evaluated at the time of diagnostic workup and divided into two categories.
Complication

The criterion for major complication is the presence of one of the following conditions attributed to Takayasu’s disease (groups IIb and III in our previous reports)\textsuperscript{5,6}:(1) microaneurysm formation (stage 2 retinopathy according to the Uyama-Asayama classification),\textsuperscript{11}(2) the brachial pressure of $\geq$200 mm Hg systolic or $\geq$110 mm Hg diastolic. Alternatively, the popliteal pressure of $\geq$230 mm Hg systolic or $\geq$110 mm Hg diastolic may be used, (3) grade 3+ or 4+ aortic regurgitation according to the aortographic classification by Sellers et al,\textsuperscript{12} and (4) angiographic demonstration of an aortic or arterial aneurysm with a diameter more than twice the normal. Patients with two or more of these complications (Takayasu’s retinopathy, secondary hypertension, aortic regurgitation, and aortic or arterial aneurysm) are also classified into the major complication group even if each of the complications is less severe than defined above.\textsuperscript{6}

Pattern of Clinical Course

If the past clinical course was marked by the development of progressively severe symptoms after a period of years since the onset, it was classified as a progressive course (patterns C and D, or crescendo symptom patterns in our previous report).\textsuperscript{7} The presenting symptoms included easy fatigability in the limbs, dizziness, blurred vision, arthralgia, neck pain, general fatigue, dyspnea, syncopal attacks, headache, and fever, particularly the latter five often produced severe symptoms. The severity of all symptoms was assessed by the common scale of restrictions on physical activity. If desk work was barely possible to perform (score 8),\textsuperscript{7} the symptom was defined as severe.\textsuperscript{7}

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR; Westergren) was measured as an index of inflammatory activity of the disease and was evaluated before corticosteroid therapy was started. When ESR was consistently $\geq$20 mm/h or $<20$ mm/h, the inflammatory activity was defined as the active and inactive stage, respectively.\textsuperscript{10}

Calendar Year of Diagnosis

In 1975, a nationwide survey of patients with this disease was conducted by the Aortitis Syndrome Research Committee in Japan.\textsuperscript{13} Since that time, patients received financial aid to pay for treatments; therefore, they were divided into earlier and recent groups, depending on the time of diagnosis.

Follow-up

The patients were prospectively followed up starting in May 1957 and continuing through December 1990 or death. The median follow-up period was 13 years 2 months, with a range of 1 month to 34 years. Of the 120 patients, 96 were examined by one of the authors every 6 weeks or at shorter intervals. Of the remaining 24 patients, 21 were followed up in the same manner for the first 5 years, after which 14 were examined at least once a year, whereas the other 7 were mainly seen by referring physicians. The remaining 3 patients were exclusively followed by referring physicians after a few years of examinations in our outpatient clinic. Information on these 10 patients was obtained once a year from the referring physicians, the patients, or both. No patient was lost to follow-up.

Treatment

During the follow-up period, oral prednisolone was prescribed in the active inflammatory stage of the disease; of the 92 patients in this stage, 80 were treated with prednisolone. Details on the prednisolone therapy have been reported elsewhere.\textsuperscript{14} Short- or long-term oral anticoagulant therapy was given to 49 patients, and acetylsalicylic acid also was often prescribed. Antihypertensive agents, digitalis, coronary vasodilators, and antibiotics were prescribed, as indicated.

Of the 120, 14 patients (11.7%) underwent surgical treatment. An aortoarterial bypass graft was placed in 4 patients: for coarctation of the thoracic aorta in 3 and for ruptured aneurysm of the thoracoabdominal aorta, which occurred in one patient after left nephrectomy. Apicoaortic bypass was performed for 1, aortorenal bypass graft for 2, aneurysmectomy of the ascending aorta for 1, a patch graft to the abdominal aorta for 1, cervical arterial reconstruction for 3, aortic valve replacement for 1, and right nephrectomy alone for 1 patient.

Statistical Analysis

The cumulative survival rates after the diagnosis were estimated using the Kaplan-Meier method,\textsuperscript{15} and differences in survival rates between groups were assessed by the log-rank statistic\textsuperscript{16} and by the 95% confidence interval.\textsuperscript{17} To determine the prognostic values of the six clinical variables, univariate and multivariate Cox regression analyses\textsuperscript{18} were performed using the Statistical Analysis System (SAS Institute Inc.).\textsuperscript{19} The univariate analysis simply shows an association of each variable with survival, whereas the multivariate analysis identifies “independent” prognostic factors that cannot be replaced by other factors. An optimal combination of independent predictors was then selected by the stepwise elimination procedure. The regression coefficients of the predictors thus selected were used to obtain a prognostic score for each patient. Calculation is made by summing up the regression coefficients of all factors present in the patient. The greater the score, the poorer was the prognosis. Grouping by this score represents a prognostic classification. Also, another attempt was made to determine the best classification. With the aid of a computer, as many classifications as theoretically feasible were produced by combining different categories of the independent predictors.\textsuperscript{20} The best classification was then selected using two criteria, i.e., the Akaike Information Criterion (AIC)\textsuperscript{20,21} and the linear trend $\chi^2$ statistic.\textsuperscript{22} When the AIC was used, the best classification was the one with the smallest AIC value, whereas for the latter, the one with the greatest $\chi^2$ values was selected. For calculation of the AIC value, patients were classified by stage and cross-classified into two outcome groups: death within 10 years and survival longer than 10 years; those followed for shorter periods were excluded.

Results

Overall Survival

During the follow-up period, there were 16 deaths related to Takayasu’s disease. All deaths occurred within 15 years after the diagnosis—10, 1, and 5 deaths during the first, second, and the last 5-year periods, respectively. This means that there are two peaks of hazard: a larger one in the early period and a smaller one in the late phase. The overall survival rate at 15 years after the diagnosis was 82.9%, and there was no death thereafter during the follow-up (Fig 1). The major causes of death were congestive heart failure in 5 patients, including one sudden death and another death during hemodialysis following right nephrectomy, acute myocardial infarction subsequent to congestive heart failure in 2 patients, cerebrovascular accidents in 4, postoperative complications in 3, and other causes in 2. The median age at the time of death was 48 years (range, 21 to 65 years). Another patient died of cancer of the uterine cervix at the age of 70 years. At the end of the follow-up in December 1990, the median age of the remaining 103 survivors was 43 years (range, 16 to 72 years). In the 120 patients, the median ages at the time of diagnosis and of disease onset were 29.5 years.
(range, 8 to 64 years) and 21 years (range, 8 to 41 years), respectively. The median delay between onset and diagnosis was 4.9 years (range, 1 month to 40.3 years).

**Comparison of Survival Between Groups**

The 120 patients were divided into two groups based on the dichotomous variables, and differences in the 15-year survival were examined (Table 1). When the life-table analyses were used, five of these variables were statistically significant predictors of survival; prognostically unfavorable indicators were the presence of major complication, progressive course, older age group (>35 years), longer delay between onset and diagnosis (>2 years), and earlier patients (1957 through 1975) (Fig 2). The lower survival rate for the earlier group could in large part be explained by a greater proportion of prognostically unfavorable patients. This was confirmed by the Wilcoxon rank sum test comparing the Cox prognostic score between the two groups (P<.001).

**Univariate and Multivariate Analyses**

The univariate Cox analysis revealed that of the six dichotomous variables, four were statistically significant predictors, including the complication, pattern of the

### TABLE 1. Comparison of Survival Rates by Clinical Variables at Diagnosis

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients (%)</th>
<th>15-Year Survival Rate, %</th>
<th>95% Confidence Interval of Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>120 (100)</td>
<td>82.9</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35</td>
<td>85 (70.8)</td>
<td>92.7</td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>35 (29.2)</td>
<td>58.3</td>
<td>12.1-56.7</td>
</tr>
<tr>
<td>Delay between onset and diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>37 (30.8)</td>
<td>97.1</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>83 (69.2)</td>
<td>77.5</td>
<td>7.6-31.6</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>92 (76.7)</td>
<td>86.9</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>28 (23.3)</td>
<td>72.2</td>
<td>−5.2-34.5</td>
</tr>
<tr>
<td>Major complication, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>69 (57.5)</td>
<td>96.4</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>51 (42.5)</td>
<td>66.3</td>
<td>14.1-46.2</td>
</tr>
<tr>
<td>Progressive course, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>73 (60.8)</td>
<td>92.9</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>47 (39.2)</td>
<td>67.9</td>
<td>7.8-42.1</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1957–1975</td>
<td>60 (50.0)</td>
<td>79.9*</td>
<td></td>
</tr>
<tr>
<td>1976–1990</td>
<td>60 (50.0)</td>
<td>96.5*</td>
<td>4.9-28.4</td>
</tr>
</tbody>
</table>

ESR indicates erythrocyte sedimentation rate (Westergren).

*14-year survival rate.
past clinical course, age of the patient, and year of diagnosis. Use of the multivariate Cox regression analysis showed only two factors (the presence of major complication and progressive course) to be significantly associated with the outcome. However, the stepwise elimination procedure revealed that in addition to these two factors, the ESR contributed to the optimal prediction of the long-term outcome. The regression coefficients of these variables were 2.454, 1.875, and 0.848, respectively.

**New Prognostic Classification**

Using the above three independent predictors in various combinations, a total of 1822 classifications were theoretically feasible, with the number of stages ranging from two to eight; i.e., the highest stages ranged from stage 2 to stage 8. As shown in Table 2, the best classification selected by the AIC was a three-stage classification involving the three independent predictors, a finding that is consistent with the result of the Cox stepwise regression analysis; a higher stage always has a greater prognostic score than the lower stages. When the linear trend $\chi^2$ statistic was used as a selection criterion, four classifications were selected, with equal $\chi^2$ values. They all had seven stages, and the only difference between them and the classification by the Cox prognostic score was that in the former, two of the latter stages were combined to form one stage.

The 15-year survival curves of patients in these three stages are depicted (Fig 3). Among them, an overall comparison showed a highly significant difference ($P<.001$, log-rank $\chi^2=37.4$). According to this new classification, patients with both major complication and progressive course (stage 3) had the worst prognosis (43% survival at 15 years), whereas for patients with neither or patients with a progressive course but elevated ESR (stage 1), the survival rate was 100% at 15 years.

**Medical Versus Surgical Treatments**

The group of patients who underwent surgery had a major complication more often than did those receiving medical treatment alone. To adjust for this imbalance, only 51 patients with a major complication were studied, including 11 patients surgically treated and 40 receiving medical treatment alone. The respective 15-year survival rates were 46.7% and 70.4% (Fig 4), with no statistical difference (95% confidence interval, $-21.2\%$ to $+68.6\%$).

**Discussion**

**Determinants of Outcome and Prognostic Classification**

The results of our present investigation are in agreement with our previous studies and the report of Subramanyan et al; a major complication and a progressive course are the two major determinants of a long-term outcome. Although the ESR per se was not a significant predictor, it added to prognostic information when combined with the above two factors, a common result obtained by the two different methods. An elevated ESR associated with a favorable prognosis may be interpreted as indicating that the disease is still in its active phase and amenable to treatment. One of the questions that must be answered in formulating a prognostic classification is the number of stages of the disease to be included. From the practical point of view, seven or eight stages are too many, and the three-stage classification based on AIC can be recommended as the most appropriate classification obtainable.

Of our recent 60 patients, the proportion of major complication group was 35% compared with 25% of 32

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**Table 2. Comparison of Two Prognostic Classifications of Takayasu's Disease**

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
<th>Stage 6</th>
<th>Stage 7</th>
<th>Stage 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complication</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>Progressive course</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>Low ESR (&lt;20 mm/h)</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

Classification by Cox regression analysis

- **Prognostic score**:
  - Stage 1: 0
  - Stage 2: 0.85
  - Stage 3: 1.88
  - Stage 4: 2.45
  - Stage 5: 2.75
  - Stage 6: 3.30
  - Stage 7: 4.33
  - Stage 8: 5.18

- **15-Y survival rate**:
  - Stage 1: 100%
  - Stage 2: 100%
  - Stage 3: 100%
  - Stage 4: 87.9%
  - Stage 5: 77.8%
  - Stage 6: 75.0%
  - Stage 7: 50.7%
  - Stage 8: 25.0%

Classification by AIC

- **Stage 1**: 100%
- **Stage 2**: 83.6%
- **Stage 3**: 43.0%

ESR indicates erythrocyte sedimentation rate (Westergren); AIC, Akaike Information Criterion. $-$, absent; and $+$, present. *See Fig 3.

![Fig 3. Comparison of survival curves of patients in three stages by our proposed new prognostic classification. Log-rank test showed highly significant differences between groups (overall, $P<.001$; stage 1 vs 2, $P<.01$; stage 1 vs 3, $P<.005$; and stage 2 vs 3, $P<.005$). Number of patients (pts) alive at the beginning of each follow-up interval is given in parentheses.](http://circ.ahajournals.org/content/90/4/1858)
patients from North America\textsuperscript{23} and 58\% of 88 patients from India.\textsuperscript{8} The overall 5-year survival rates of these series were 96.5\%, 94\%, and 80.3\%, respectively. Thus, a decrease in survival across different populations may be partly explained by higher proportions of patients with a major complication.

\section*{Year of Diagnosis}

The survival of patients with Takayasu's disease has tended to improve since 1985\textsuperscript{23-28} compared with during the 1970s\textsuperscript{2,3,29-34} However, our present study revealed that there is a significant bias in the prognostic score between the earlier and recent groups. This may be the result of increasing knowledge of Takayasu's disease since 1975 and a major factor accounting for the improved survival.

\section*{Medical Versus Surgical Treatments}

In the present investigation, we found no significant difference between the 15-year survival rate for patients treated medically and the rate for those treated surgically in the major complication group (Fig 4), although the number of the latter is too small to arrive at a valid conclusion. Recently, however, several surgical studies on this disease revealed favorable results.\textsuperscript{25-28} In the large series of Tada et al\textsuperscript{28} in which vascular reconstruction was done for 93 patients during the 32 years from 1959 through 1991, there were nine surgical deaths, but eight were operated on before 1970. Therefore, in the major complication group, particularly in patients with a combination of major complication and progressive course (stage 3), not only aggressive medical treatment but also surgical intervention may be considered, although criteria for indication for surgical intervention in this disease are not established.

In contrast, in our group with no major complications, the 15-year survival rate was 96.4\%, and only 3 patients (4.3\%) had surgical treatment. Concerning the efficacy of corticosteroid therapy in the active inflammatory stage, there have been positive\textsuperscript{2,6,14,23,31,35-38} and less positive\textsuperscript{2,24,26} results. However, in patients with this disease, improvement in stenosed arteries\textsuperscript{14,35,37} and a decrease in the thickening of the arterial wall\textsuperscript{39,40} during corticosteroid therapy have been increasingly reported, whereas spontaneous improvement of the involved arteries was documented only for three cases.\textsuperscript{14,41,42}

Therefore, most patients without a major complication may be good candidates for medical rather than surgical treatment.

\section*{Implications}

For patients with Takayasu's disease, complications, pattern of clinical course, and ESR are not only important predictors of survival for individual patients but can serve to adjust for imbalance when survival rates in different patient populations are compared. Patients with poor prognostic indicators, particularly those with a combination of major complication and progressive course (stage 3), may require more aggressive management and close follow-up than do those without these manifestations. A 10-year follow-up after the diagnosis may not be long enough. When feasible, the diagnosis should be made at the time when there is neither a major complication nor a progressive course or when the course is progressive and the ESR is elevated (stage 1).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|}
\hline
Group & No. & 0 & 2 & 4 & 6 & 8 & 10 & 12 & 14 & 16 \\
\hline
Medically treated & (40) & 100 & 80 & 60 & 40 & 20 & 0 & 0 & 0 & 0 \\
Surgically treated & (37) & 100 & 80 & 60 & 40 & 20 & 0 & 0 & 0 & 0 \\
Medical and surgically treated & (27) & 100 & 80 & 60 & 40 & 20 & 0 & 0 & 0 & 0 \\
\hline
\end{tabular}
\caption{Comparison of survival curves of patients with a major complication and treated medically and those with the same stage and treated surgically. The difference in survival rate was not statistically significant (95\% confidence interval, $-21.2\%$ to $+68.6\%$). Number of patients (pts) alive at the beginning of each follow-up interval is given in parentheses.}
\end{table}

\section*{References}


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