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Coronary artery outcomes among children with Kawasaki disease in the United States and Japan


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A B S T R A C T

Objective: It has been claimed that the aneurysm rate for Kawasaki disease (KD) patients in Japan is lower than in the U.S. However it has been difficult to compare coronary artery (CA) outcomes between the two countries because of different definitions for CA abnormalities. Therefore, we compared CA internal diameters between Japanese and U.S. KD patients using standard definitions and methods.

Study design: We retrospectively reviewed CA outcomes in 1082 KD patients from 2 centers in the U.S. and 3 centers in Japan and compared Z-max scores (maximum internal diameter for the left anterior descending or right coronary artery expressed as standard deviation units from the mean (Z-score) normalized for body surface area) obtained within 12 weeks after onset and calculated using two different regression equations from Canada (Dallaire) and Japan (Fuse). We defined a Z-max of ≥2.5 as normal and a Z-max of ≥10 as giant aneurysm.

Result: The median Z-max for the U.S. and Japanese subjects was 1.9 and 2.3 SD units, respectively (p < 0.001). There was no significant difference in rates of patients with Z-max ≥ 5.0 between the countries. In a multivariable model adjusting for age, sex, and treatment response, being Japanese was still associated with a higher Z-max score.

Conclusion: Previously reported differences in aneurysm rates between Japan and the U.S. likely resulted from use of different definitions and nomenclature. Adoption of Z-scores as a standard for reporting CA internal diameters will allow meaningful comparisons among different countries and will facilitate international, collaborative clinical trials.

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1. Introduction

In the era before the use of intravenous immunoglobulin (IVIG) to treat children with Kawasaki disease (KD), aneurysm rates of approximately 25% were noted both in Japan and the U.S. [1–3]. KD is now the most important cause of acquired heart disease in children in the developed world and more than 60 countries in Asia, the Middle East, the U.S., Africa, and Europe have reported KD cases [4–6]. Reported rates of coronary artery (CA) aneurysms vary widely among KD patients from different countries [7–16]. Currently, studies from the U.S. report an aneurysm rate of approximately 4.0–5.0% [7,17], while rates for Japan are reported to be on the order of 1.0% [9]. To clarify whether this is a problem of semantics (different definitions of aneurysms), a real difference stemming from different clinical practices (timing of echocardiograms or timing of IVIG administration), or differences in host genetics, we conducted a comparative study.
among two centers in the U.S. and three centers in Japan over the same time period and used the internal diameter of the coronary artery normalized for body surface area (Z-score) as a standardized assessment tool to compare outcomes.

2. Methods

2.1. Patient population

Patients with KD included in this study met the case definitions of the American Heart Association (AHA) for the U.S. sites (Rady Children’s Hospital San Diego and Boston Children’s Hospital) or the Japanese Circulation Society (JCS) for the Japanese sites (Toho University Omori Medical Center, Kitasato University Hospital, and Juntendo University Urayasu Hospital; Table 1) [18,19]. The records of unselected, consecutive KD patients treated at the five participating centers during the 4-year period from January 1, 2004 through December 31, 2008 were retrospectively reviewed. Subjects were included regardless of illness day at diagnosis or the timing of treatment. Patients diagnosed and treated at outside hospitals and referred to the study centers for additional treatment or evaluations were excluded. The study was reviewed and approved by the Institutional Review Boards of the participating centers.

2.2. Data collection

Data were collected on standardized forms at each of the participating sites and included sex, age, body surface area, illness day at diagnosis, and treatment with a single or more than one infusion of IVIG. Illness Day 1 was defined as the first day fever. Late treatment was defined as IVIG administration after the 10th day of illness. Incomplete KD was defined as fever for ≥5 days associated with 2 or 3 of the principal clinical features of KD associated with abnormalities by echocardiogram [18–20].

2.2.1. Echocardiographic data

Although procedures for obtaining echocardiographic measurements were not formally standardized among centers, each center followed the recommended guidelines for their country (AHA or JCS). Only the AHA guidelines specify obtaining the cross-sectional measurement of the internal diameter 5 mm from the origin of the arterial segment. The maximal internal diameter (mm) of the left anterior descending coronary artery (LAD) and the right coronary artery (RCA) within 12 weeks after onset was obtained from each center. The diameter of left main coronary artery was excluded because of the wide range of anatomic variants in this arterial segment that often preclude accurate measurement of the internal diameter [21]. Patients’ height (cm) and weight (kg), corresponding to the echo date of the largest arterial segment that often preclude accurate measurement of the internal diameter was also obtained.

2.2.2. Z-score equations

Body surface area (BSA) was computed by both the Du Bois and Haycock equations and compared [22–24]. The Z-score was computed using two different equations, both normalized for body surface area. The Z-score calculator (ZSP Version 9) was based on measurements from over 4000 normal Japanese children (http://www.zscore.jp/). The calculator classifies Z scores only up to a value of 8.2 SD units so it therefore could not be used for comparisons of Z score as a continuous variable. The Dallaire equation was calculated based on 1033 normal Canadian children [25]. Z-max was defined as the maximum Z-score for the LAD or RCA measured by echocardiography within 12 weeks after fever onset. We analyzed Z-max as a continuous variable and as a categorical variable (-2.5, ≥2.5–5.0, ≥5.0, and ≥10) based on previously published cutpoints using the Canadian equation [26].

Table 1

Comparison of published standards of coronary artery abnormalities assessed by echocardiography in the U.S. and Japan.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>U.S. (n = 568)</th>
<th>Japan (n = 514)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, months (IQR)</td>
<td>30.6 (15.6–55.9)</td>
<td>24.6 (12.0–43.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median BSA, m² (IQR)</td>
<td>0.60 (0.47–0.73)</td>
<td>0.53 (0.44–0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>351 (61.9)</td>
<td>308 (59.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Median Illness day, day (IQR)</td>
<td>6 (5–9)</td>
<td>5 (4–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incomplete KD, n (%)</td>
<td>90 (15.9)</td>
<td>158 (30.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients treated with single IVIG, n (%)</td>
<td>523 (92.1)</td>
<td>468 (91.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients treated with &gt;1 IVIG, n (%)</td>
<td>26 (4.6)</td>
<td>24 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Late treatment, n (%)</td>
<td>62 (11.5)</td>
<td>67 (12.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Subjects treated with &gt;1 IVIG, n (%)</td>
<td>109 (20.1)</td>
<td>126 (25.8)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

BSA = Body surface area calculated using the Du Bois equation, KD = Kawasaki disease, Illness Day 1 = First day of fever, IVIG = Intravenous immunoglobulin, Late treatment = Treatment after Illness Day 10, NS = not significant.

2.3. Statistical analysis

Descriptive analyses were performed to compare U.S. versus Japanese KD patients. Medians and interquartile ranges (IQRs) were reported for continuous variables and frequency counts and percentages were reported for categorical variables. Univariate tests of significance were computed via Wilcoxon Rank Sum test for continuous variables and Fisher’s exact test for categorical variables. Pearson’s correlation was used to compare the two BSA and the two Z-score methods. Multivariable regression was performed to compare Z-max scores between U.S. and Japanese patients, adjusting for age, gender, illness days, treatment, and treatment response. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed in R (http://cran.r-project.org), version 2.14.0.

3. Results

3.1. Study population characteristics

A total of 1082 subjects were included with 568 from the U.S. and 514 from Japan (Table 2). U.S. subjects were older, were treated on average one day later, and were more likely to be treated after Illness Day 10 as compared to Japanese subjects (p < 0.001 for all comparisons). Japanese subjects were more likely to be classified as clinically incomplete cases (p < 0.001) and were more likely to receive additional infusions of IVIG (p = 0.03).

3.2. CA outcomes

The median BSA calculated by either the Du Bois or Haycock equations was higher for the U.S. versus the Japanese subjects, consistent with the older age of the U.S. subjects (p < 0.001, Table 2). BSA values calculated by the Du Bois equation strongly correlated with values calculated by the Haycock equation (r = 0.998). Values for Z-max calculated using the two different BSA equations also showed a strong positive correlation (r = 0.999).

The Z-max calculated using the Dallaire equation was compared between the U.S. and Japanese subjects both as a continuous and as a categorical variable (Figs. 1 and 2). The median Z-max calculated by the Dallaire equation for U.S. and Japanese KD subjects was 1.9 (IQR 1.4–2.7) and 2.3 (IQR 1.5–3.1) SD units, respectively (p < 0.001; Fig. 1). Using either the Fuse or the Dallaire Z-score equations, a higher percentage of U.S. subjects had normal coronary arteries (Z-max < 2.5, p < 0.001) and a higher percentage of Japanese subjects had a Z-max between 2.5 and 5.0 (p < 0.001). Using either
equation, there was no significant difference in rates of Z-max ≥ 5 or ≥ 10 between subjects in the two countries (Z-max ≥ 10, n (%): U.S.: 15 (2.6), Japan: 7 (1.4); Fig. 2).

The absolute measurement of CA internal diameters was compared between subjects less than 5 years of age from the two countries, which included 77.8% of the U.S. subjects and 86.8% of Japanese subjects. The median maximal internal diameter was identical (2.3 mm) between subjects from the two countries. Similarly, there was no significant difference in the percentage of subjects classified as having transiently dilated, >3–≤4 mm, or >4 mm CA based on the JCS guidelines (Transient dilatation: U.S.: 23 (7.4%), Japan: 19 (5.2%); Maximal internal diameter >3–≤4 mm: U.S.: 62 (10.9%), Japan: 42 (8.2%); >4 mm: U.S.: 24 (4.2%), Japan: 15 (2.9%)).

Multiple linear regression analysis was performed to identify independent risk factors for Z-max. The model demonstrated that younger age, male sex, late treatment, failure to respond to initial IVIG infusion, and being Japanese were independent risk factors for a higher Z-max (Table 3). In other words, after adjusting for age, sex, and treatment response, Japanese patients still had a higher Z-max score compared to U.S. patients.

4. Discussion

This is the first study to directly compare CA outcomes in Japanese and American KD patients using standardized definitions across populations. The median Z-max was significantly higher for Japanese subjects using the Dallaire Z-score equation. When analyzed as a categorical variable, there was no difference in the rate of patients with Z-max scores ≥ 5.0 or ≥ 10.0 using this definition. A higher percentage of Japanese children were classified as having at least one coronary artery segment with a Z-max ≥ 5.0, regardless of the Z-score method used. Use of Z-score equations formulated based on either Japanese or North American children had no effect on the results. Predictors of a higher Z-max score included younger age, male sex, late treatment, and IVIG-resistance as has been previously reported [7,20,27]. Despite adjusting for these factors, Japanese KD patients were still more likely to have a higher Z-max. Among the U.S. patients, there were fewer than five Japanese subjects. Therefore, there was little overlap between the U.S. and Japanese groups and these results may reflect true genetic differences in susceptibility to coronary artery damage [28,29].

Although it has been frequently claimed that aneurysm rates in U.S. children are higher than in Japanese children, our findings do not support this claim [7,9,17,19]. The CA aneurysm rate has been reported from several countries, but the timing of echocardiography during the illness has varied and the use of Z-scores has not been widely adopted, thus making meaningful comparisons across populations difficult [7–16]. Indeed, comparing rates from these published reports can lead to erroneous conclusions regarding possible genetic differences in response to IVIG or to susceptibility to aneurysm formation [28,29]. Our results suggest that use of different CA definitions may have led to false conclusions about rates of CA aneurysms in the U.S. and Japan. Two different equations were used for calculating Z-score to evaluate and compare their performance. The Fuse equation was created based on the size of CAs of over 4000 healthy Japanese

<table>
<thead>
<tr>
<th>β</th>
<th>Standard error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.007</td>
<td>0.002</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.502</td>
<td>0.145</td>
</tr>
<tr>
<td>Illness day at diagnosis</td>
<td>0.032</td>
<td>0.030</td>
</tr>
<tr>
<td>Complete or incomplete KD</td>
<td>0.120</td>
<td>0.175</td>
</tr>
<tr>
<td>Late treatment</td>
<td>0.979</td>
<td>0.380</td>
</tr>
<tr>
<td>IVIG non-responder</td>
<td>1.656</td>
<td>0.171</td>
</tr>
<tr>
<td>Japan</td>
<td>0.347</td>
<td>0.155</td>
</tr>
</tbody>
</table>

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children. These data were analyzed with the least mean squares (LMS) method [23,30,31]. The Dallaire Z-score equation was created based on 1033 healthy children in Canada [25]. The clear advantage of using Z-scores for the evaluation of CA dimensions in the pediatric population is the normalization for BSA and the use of specific criteria for right and left CAs [25,32–34]. The distribution of Z-max scores ≥5.0 was slightly different between the two methods (Fig. 2). This underscores the importance of using the same Z-score method for sequential measurements on the same patient over time.

To estimate the BSA, we were forced to use Du Bois equation for the Fuse Z-score because this equation is integrated into the Z-score Calculator (ZSP version 9). However, the Du Bois equation was based on adult subjects and one individual with short stature secondary to hypothyroidism and it is known to be inaccurate for infants younger than 3 months and neonates [22]. Fortunately, the older age of the majority of our KD subjects resulted in an excellent correlation when comparing BSA calculated using either the Du Bois or the Haycock equations [24]. A similar conclusion was reached by Dallaire and colleagues who also found good concordance between the two equations [25].

This study revealed not only differences in coronary outcome between the two countries, but also highlighted differences in medical practice. While Illness day at diagnosis was later and the number of late treatment cases was higher in the U.S. study population, a diagnosis of incomplete KD and failure to respond to medical practice. While Illness day at diagnosis was later and the diagnosis and management of KD patients. Our study underscores the importance of using the same Z-score method for sequential measurements on the same patient over time...

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