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Clinical Features Differ Substantially Between Caucasian and Asian Populations of Marfan Syndrome

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Background: Prevention of aortic dissection and sudden death in patients with Marfan syndrome (MFS) requires accurate diagnosis. MFS is diagnosed by the Ghent criteria, which are primarily based on clinical features of Caucasian MFS populations. We determined whether the Ghent criteria apply to Asian MFS populations.

Methods and Results: In this multicenter study, we included 255 adult MFS patients according to the Ghent criteria of 2010. Patients were excluded if they were neither Caucasian nor Asian. The Asian MFS population (n=49) had a smaller body surface area (BSA: 1.8 m^2 vs. 2.0 m^2, P<0.001), a more severely affected aortic root (absolute aortic diameter: 42.9 mm vs. 43.3 mm, P=0.802; corrected for BSA: 24.9 mm vs. 21.7 mm, P<0.001; Z-score: 4.5 vs. 3.6, P=0.013), and more often a positive systemic score (75.5% vs. 60.0%, P=0.045), but less frequently ectopia lentis (24.5% vs. 48.1%, P=0.004) compared with the Caucasian population (n=206).

Conclusions: The Ghent criteria do not necessarily apply to Asian MFS populations, resulting in a more severely affected cardiovascular system. This may be related to under diagnosis of MFS by multiple factors, including the use of Z-score, and genetic and racial differences. The Ghent criteria should be adapted for Asian populations in order to accurately diagnose MFS. (*Circ J* 2013; **77:** 2793–2798)

Key Words: Diagnosis; Ethnicity; Ghent criteria; Marfan syndrome

Marfan syndrome (MFS) is a monogenic connective tissue disorder, mainly caused by mutations in the gene encoding for fibrillin-1 (*FBN1*),[1] which leads to increased release of transforming growth factor-β.[2–4] Patients with MFS suffer from an increased risk of cardiovascular manifestations such as aortic root dilatation, mitral valve prolapse (MVP), impaired biventricular function, and aortic dissection, the latter being the main cause of sudden death.[5–10] Pregnant women need particular attention, because of the high risk for aortic dilatation or dissection during and/or after pregnancy.[11–13] Prevention of these cardiovascular complications requires accurate diagnosis,[14,15] which is currently guided by the Ghent criteria.[16] In the Ghent criteria, MFS is diagnosed by genetic testing and more than 20 different clinical features, predominantly based on the Caucasian race.[16] However, MFS is equally prevalent all over the world,[17] without specific diagnostic criteria for races other than Caucasian.

Currently, the general Asian population accounts for more than one-fifth of the total world population.[18] Previous research has shown that some clinical features of MFS, such as myopia and scoliosis, are more frequently present in the general Asian population.[19,20] In addition, a study that included Korean and Japanese MFS patients revealed differences in clinical features compared with Caucasian MFS populations.[21,22] Furthermore, genetic testing is not performed on a routine basis in some Asian countries such as Singapore, adding even more weight to the accuracy of the Ghent criteria with regard to the clinical features in order to establish a reliable MFS diagnosis.

If the clinical MFS features differ between Asian and Caucasian MFS populations, the Ghent criteria may need adjustment in order to prevent delayed diagnosis and thereby prevent cardiovascular complications. The aim of our study was to system-

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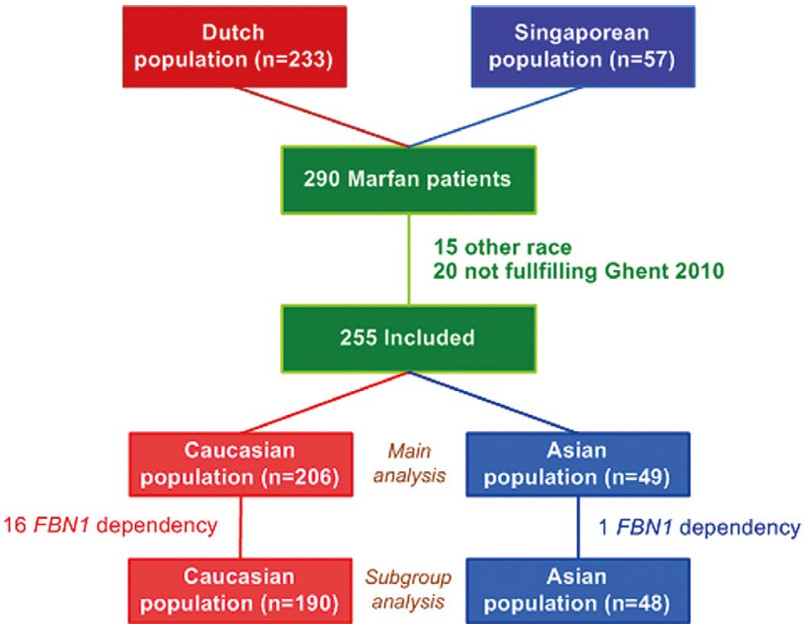

Figure 1. Flow chart of inclusion of adult Marfan patients from a Dutch and Singaporean population for main and subgroup analyses.

atically compare the clinical features between a Caucasian and an Asian MFS population.

In this study we addressed the following research questions: (1) Which of the cardiovascular, ocular and skeletal features differ between Caucasian and Asian MFS populations? (2) Do the observed differences between the Caucasian and Asian MFS populations reveal that the Ghent criteria need adjustment for Asian populations?

Methods

Patient Populations

In this retrospective multicenter study, we collected all relevant clinical and genetic data of patients from a Dutch and a Singaporean MFS cohort. The Dutch patients were participants of the COMPARE study, which is a multicenter randomized clinical trial investigating the effects of losartan on aortic dimensions.[23] All patients were enrolled through Marfan screening clinics at the 4 university hospitals in the Netherlands. Inclusion criteria were MFS according to the Ghent criteria of 1996 and adults aged 18 years or more. Patients were ineligible if they were already using an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, had renal dysfunction, had an aortic root diameter >50 mm, had a history of aortic dissection, or were planned for aortic surgery within 6 months of inclusion in the study.

The Singaporean patients were collected from the Marfan screening clinic of the National University Hospital in Singapore. In that clinic, absolute aortic diameter was used for diagnosis of MFS, and we retrospectively calculated the Z-scores for these patients. Furthermore, we retrospectively excluded Singaporean patients not fulfilling the inclusion and exclusion criteria at the start of the COMPARE study (year 2008). For this study we also excluded all patients not fulfilling the Ghent criteria of 2010. Furthermore, we excluded patients if they were neither Caucasian nor Asian (Figure 1). Because genetic screening was not available for the Singaporean MFS population, an additional subgroup analysis was performed with only Caucasian patients who did not have a *FBN1* mutation to fulfill the Ghent criteria.

Clinical Features

The available data included cardiovascular, ocular and skeletal features of MFS, which were determined by medical specialists at the attending hospital. Extended physical examination was performed by the clinical genetics departments. The aortic root diameter was measured in end-diastole at the level of the sinus of Valsalva by cardiologists using the leading edge to leading edge technique of echocardiography at the date of inclusion.[24,25] Eye examination was performed by ophthalmologists. Specialists in both countries identify the clinical features following the Ghent criteria of 2010.

Statistical Analysis

Data are presented as mean value±standard deviation or as number of patients (percent) where appropriate. To determine the significant differences in the clinical features between the Caucasian and Asian MFS populations, we used Student's t-test, the Mann-Whitney test or Fisher's exact test where appropriate. Similar tests were performed for the subgroup analysis. All statistical tests were 2-sided and differences were considered statistically significant at $P<0.05$. Data analysis was performed using the SPSS statistical package (19.0 for Windows; SPSS Inc, Chicago, ILL, USA).

Results

After exclusion of 15 patients because they were neither Caucasian nor Asian and 20 patients because they did not fulfill the Ghent criteria of 2010, a total of 255 MFS patients were enrolled in this study (mean age 40 years (range 19–73 years); 46% females (Figure 1). The Asian population (n=49) comprised 42 Chinese patients (85.7%), 5 Malay patients (10.2%) and 2 Indian patients (4.1%). The Caucasian population (n=206) was significantly older (41 vs. 35 years; $P=0.008$), taller (188 vs. 178 cm; $P<0.001$) and heavier (79 vs. 63 kg; $P<0.001$) than the Asian population (n=49). Table 1 shows the clinical charac-

Table 1. Characteristics of the Caucasian and Asian Marfan Study Populations

Variable	Overall (n=255)	Caucasian (n=206)	Asian (n=49)	P value
Basic features				
Female	116 (45.5)	98 (47.6)	18 (36.7)	NS
Age (years)	39.8±13.4	40.8±13.3	35.2±13.4	0.008
Length (cm)	186.2±11.7	188.0±11.2	178.5±11.0	<0.001
Weight (kg)	76.1±16.4	79.1±15.2	63.1±14.9	<0.001
Body surface area (m^2)	2.0±0.3	2.0±0.2	1.8±0.2	<0.001
β-blocker treatment	187 (73.3)	146 (70.9)	41 (83.7)	NS
Major Marfan features				
Aortic root dilatation	228 (89.4)	182 (88.3)	46 (93.9)	NS
Ectopia lentis	111 (43.5)	99 (48.1)	12 (24.5)	0.004
FBN1 mutation*	168	166 (86.4)	2 of 2	.
Skeletal score >7	160 (62.7)	123 (60.0)	37 (75.5)	0.049
Positive family history	167 (65.5)	140 (68.0)	27 (55.1)	NS

Data are mean±standard deviation or no. of patients (%).
*Of 8 Caucasian patients, *FBN1* mutation analysis was not performed.

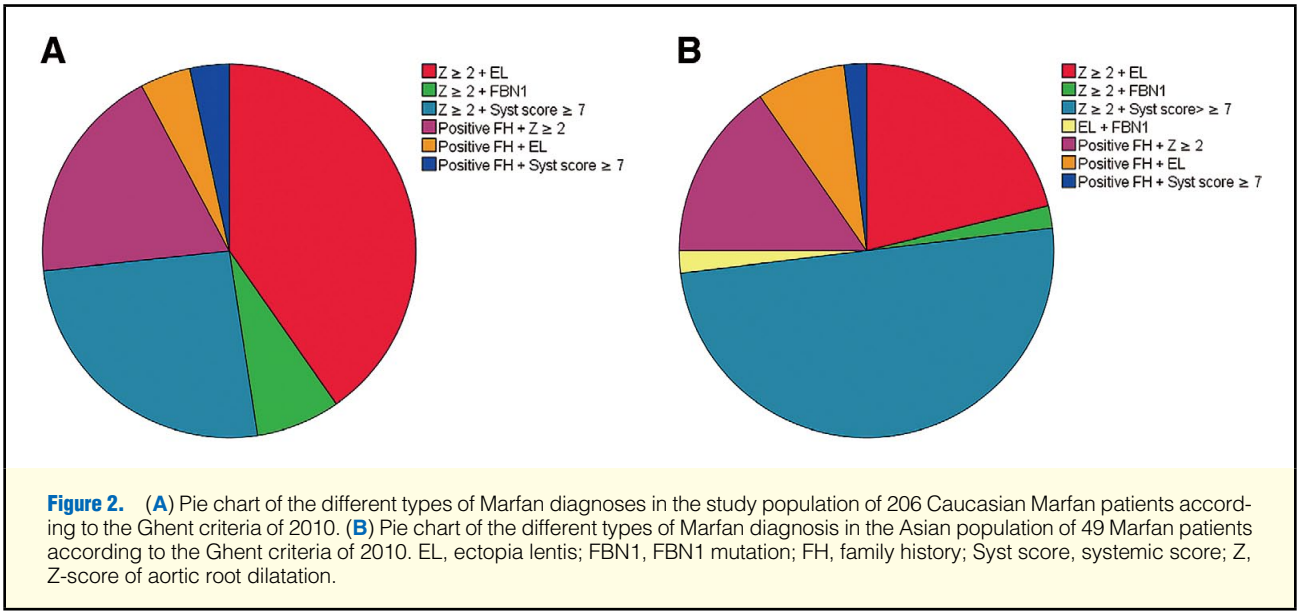

Figure 2. (**A**) Pie chart of the different types of Marfan diagnoses in the study population of 206 Caucasian Marfan patients according to the Ghent criteria of 2010. (**B**) Pie chart of the different types of Marfan diagnosis in the Asian population of 49 Marfan patients according to the Ghent criteria of 2010. EL, ectopia lentis; FBN1, FBN1 mutation; FH, family history; Syst score, systemic score; Z, Z-score of aortic root dilatation.

teristics of the Caucasian and Asian MFS populations at the time the diagnosis was established. MFS diagnosis was differently distributed in both populations. In the Caucasian population, MFS diagnosis mostly comprised aortic root dilatation together with ectopia lentis (40%, **Figure 2A**), whereas in the Asian population MFS diagnosis was mostly established by aortic root dilatation together with a positive skeletal score (47%, **Figure 2B**). Of all 255 patients, 73% used a β-blocker on a regular basis, with no significant difference in β-blocker use between groups.

Cardiovascular System

Clinical features of the cardiovascular system in MFS comprised aortic root dilatation, aortic dissection (types A and B), descending aorta dilatation and aortic surgery. Asian MFS patients had overall a more severely affected cardiovascular system than Caucasian MFS patients. There was no difference in absolute aortic root diameter between the Caucasian and Asian populations (43.3±4.7 vs. 42.9±8.5 mm, respectively, P=0.802). However, when aortic root diameter was corrected for body surface area (BSA) or when the Z-score was used, the aortic root was significantly larger among the Asian population compared with the Caucasian (24.9±5.8 mm/m^2 vs. 21.7±2.7 mm/m^2, P<0.001 and 4.5±3.2 vs. 3.6±1.7, respectively, P=0.013). No significant differences were found between groups for type B dissections, descending aorta dilatation or distal graft surgery (**Figure 3A**).

Ectopia Lentis and a Positive Family History for MFS

Besides aortic root dilatation with a Z-score ≥2, ectopia lentis and a positive family history with proven MFS are major Ghent criteria. Ectopia lentis was more prevalent in the Caucasian population (48.1% vs. 24.5%, P=0.004) compared with the Asian population (**Table 1**). There was no difference between groups in family history with proven MFS.

Systemic Score

Most skeletal features were more prevalent in the Asian popu-

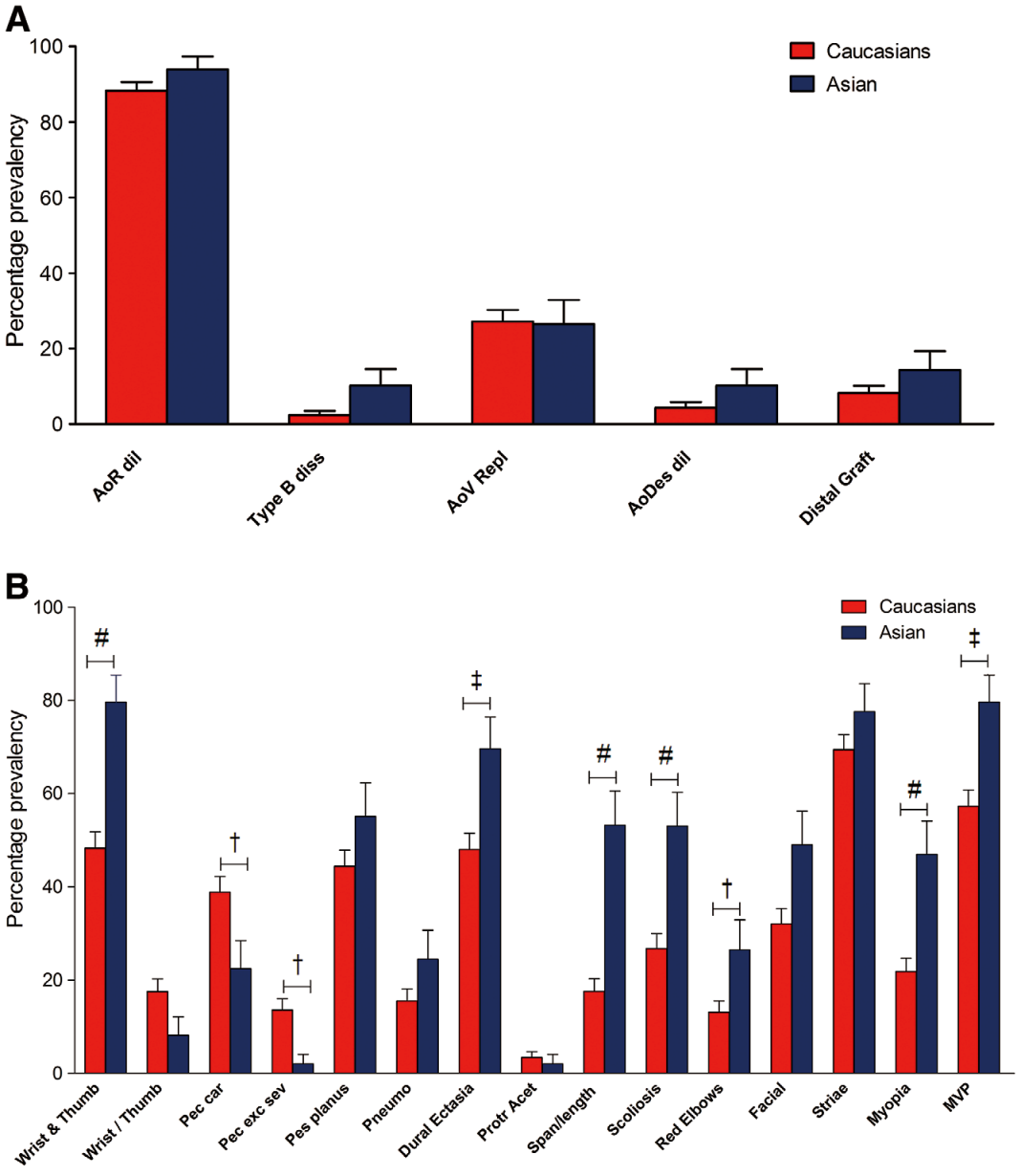

Figure 3. (**A**) Bar chart showing mean percentage of prevalence of different features of the cardiovascular system between the Caucasian and Asian Marfan populations. All values are mean + standard deviation. (**B**) Bar chart with mean percentage of prevalence of different features of the systemic score between the Caucasian and Asian Marfan population. All values are mean + standard deviation. †P<0.05; ‡P<0.01; #P <0.001. Pec car, pectus carinatum; Pec exc sev, severe pectus excavatum; Pneumo, spontaneous pneumothorax; Protr Acet, protrusio acetabuli; span/length, span/length ratio >1.05; Scoliosis, scoliosis >20 degrees; Red elbows, reduced extension of the elbows; Facial, 3/5 facial features; MVP, mitral valve prolapse.

lation, with the exception of pectus abnormalities. A positive wrist and thumb sign was seen in 80% of the Asian MFS population and 48% of the Caucasian MFS population (Figure 3B, P<0.001). In addition, an arm length/height ratio of more than 1.05 was more frequent in Asians (53% vs. 18%, P<0.001) compared with the Caucasian MFS population. Furthermore, in the Asian MFS population the prevalence of dural ectasia was higher (69% vs. 47%, P=0.008), scoliosis of more than 20% (53% vs. 27%, P<0.001), reduced extension of the elbows (27% vs. 13%, P=0.029), myopia >3 diopters (47% vs. 22%, P<0.001) and MVP (80% vs. 57%, respectively P=0.005) compared with the Caucasian MFS population (Figure 3A).

Pectus abnormalities were more prevalent in the Caucasian population, with both pectus carinatum (39% vs. 22%, P=0.032) and pectus excavatum requiring surgery (14% vs. 2%, P=0.022).

Subgroup Analysis

Subgroup analysis was performed in Asian MFS patients and Caucasian MFS patients who were not dependent on their *FBN1* mutation to fulfill the Ghent criteria of 2010. For the subgroup

Table 2. Frequency of the Involvement of Major Organ Systems

Origin	Reference	Patient no.	Age (years)	AoR dil (%)	ADiss (%)	Ocular (%)	Skeletal (%)	*FBN1* (%)
Caucasian								
Italian	Arbustini et al[26]	81	34 (18–59)	80	11	54	56	100
French	Faivre et al[28]	1,013	29 (9–34)	77	14	54	32	100
German	Rommel et al[30]	31	29 (19–40)	65	10	42	48	100
German	Soylen et al[31]	36	34 (26–42)	80	31	58	43	100
Dutch	Present study	206	41 (30–50)	88	2	48	60	83
Asian								
Japanese	Akutsu et al[21]	46	36 (30–43)	98	24	33	15	100
Japanese	Matsukawa et al[29]	12	38 (27–49)	100	31	75	100	100
Korean	Yang et al[32]	48	36 (20–69)	96*		41	63	84
Korean	Yoo et al[22]	39	29 (7–52)	95*		33	21	87
Chinese	Chung et al[27]	24	19 (13–25)	79	8	21	17	100
Singaporean	Present study	49	32 (24–45)	94	10	25	76	–

*Study did not distinguish between aortic dilatation and aortic dissection for cardiovascular involvement.
AoR dil, aortic root dilatation; Adiss, aortic dissection.

analysis, we excluded 1 patient from the Asian population and 16 from the Caucasian population. The subgroup analysis rendered similar results to those of the main analysis with regard to cardiovascular complications and differences between clinical features (data not shown).

Discussion

This study demonstrated significant differences in the clinical features of the cardiovascular, ocular and skeletal systems between a Caucasian and Asian MFS population. In particular, the cardiovascular system seemed to be more severely affected in the Asian population, with larger aortic root dimensions corrected for BSA or when Z-scores were used and more frequently MVP, while there was similar use of β-blocker therapy.

In line with previously described Caucasian and Asian Marfan populations, we confirmed that Asian Marfan populations have a higher prevalence of aortic root dilatation compared with Caucasian Marfan populations (**Table 2**).[21,22,26–32] A possible explanation for the more severely affected cardiovascular system in the Asian population may be under diagnosis of MFS because of 3 factors. The first factor is "true" racial differences between Caucasian and Asian populations in general. Some clinical features, such as myopia and scoliosis, are much more common in the general Asian population than in the Caucasian population.[33–35] Therefore, these features are less likely to be noticed, resulting in reduced MFS screening and under diagnosis. In our study, we also found a high prevalence of myopia and scoliosis in the Asian MFS population. Furthermore, our study confirmed that Asian populations have a lower prevalence of ectopia lentis and less pectus deformities.[21,22] The second factor in the under diagnosis of MFS in the present study may be that genetic testing for a *FBN1* mutation is not routine practice in Singapore, because of insurance regulations. MFS is a progressive disease, so genetic testing is important in patients who do not yet meet the Ghent criteria, such as mildly affected and young patients,[36] who may develop MFS and cardiovascular complications over time. As a result, patients will be diagnosed at a later stage of disease and therefore present with more severe features. Therefore, in countries where genetic testing is not routinely available, accurate applicability of the Ghent criteria to different races is a necessity to prevent cardiovascular complications. The third factor was the use of absolute aortic diameters in Singapore instead of Z-scores. Although the Asian and Caucasian MFS populations had similar absolute aortic root diameters, the aortic root corrected by Z-score was significantly more dilated in the Asian compared with the Caucasian MFS population. In populations with a large BSA, Z-scores seem to underestimate aortic root dilatation,[37] because the relationship between aortic root diameter and BSA is not linear but has an absolute threshold in individuals with a large BSA of approximately 38 mm. However, in populations with much smaller BSA, such as Asian populations, the Z-score seems to be more accurate in predicting the severity of aortic root dilatation. Furthermore, the Z-score is currently calculated following formulas using aortic root diameters and BSA of the Caucasian population (**Appendix**). Adjusting the formulas for Asian populations with mean BSA measurements of the general Asian population is recommended.

Although we confirmed several differences between the clinical features of an Asian and Caucasian MFS population in comparison with some smaller studies, discrepancies exist. Akutsu et al[21] and Yoo et al[22] found less involvement of the skeletal system in their Japanese and Korean MFS populations, respectively, compared with our Asian cohort. Those 2 studies had some selection bias, because most of their patients came to the hospital with an indication for aortic surgery or acute aortic dissection. Our patients were enrolled from Marfan screening clinics. Another explanation may be the lack of genetic testing in our Singaporean cohort. However, we suggest this is a minor factor, because when we excluded MFS patients who were dependent on *FBN1* mutation to fulfill the Ghent criteria of 2010, the clinical features of the Asian and Caucasian populations were essentially similar.

In conclusion, clinical features of the cardiovascular, ocular and skeletal systems significantly differ between Caucasian and Asian MFS populations. Based on the outcomes of our study, we recommend the Z-score be used for aortic root dilatation in Asian populations. Furthermore, more information about the prevalence of MFS features in the general and MFS Asian populations is needed in order to optimize the Ghent criteria for accurate diagnosis and prevention of cardiovascular complications of MFS for the Asian races. Finally, genetic testing of young and mildly affected patients is recommended in order to diag-

nose MFS before the onset of cardiovascular complications.

Disclosures

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Appendix

Z-score and mean dependent on age and BSA:
Haycock formula:

$$\text{BSA } (m^2) = 0.024265 \times \text{Height (cm)}^{0.3964} \times \text{Weight (kg)}^{0.5378}$$

Z-score for aortic root diameter:

$$Z = \frac{\text{AoD (mm)} - \text{mean (mm)}}{\text{SD (mm)}}$$

Mean aortic root diameter:

- Age <18 years : $\text{mean} = 1.02 \times (0.98 \times \text{BSA}(m^2))$
- Age <40 years : $\text{mean} = 0.97 \times (0.74 \times \text{BSA}(m^2))$
- Age >40 years : $\text{mean} = 1.92 \times (0.74 \times \text{BSA}(m^2))$

BSA, body surface area (m^2); Z, Z-score; AoD, aortic root diameter (mm); mean, mean aortic root diameter in general population dependent on age and body surface area (mm); SD, standard deviation (mm).