Anatomical characteristics of patients with symptomatic severe aortic stenosis in China

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With accumulating evidence of transcatheter aortic valve replacement (TAVR) worldwide, it is gradually realized that patients being treated are different across different countries, including but not limited to their age, habitus, disease etiology, aortic valve morphology, and sizes of structures.[1] In China, the average age of TAVR patients is around 5 years younger than industrialized countries,[2] making Chinese patients a good predictive sample of what the industrialized countries might see in TAVR screening in the near future due to the expansion of this technique to younger patients, but anatomical features appreciated from multislice computed tomography (MSCT) in the Chinese patient population have not been well demonstrated.

We conducted a retrospective analysis from 54 centers in China, including patients with native severe aortic stenosis being sent for TAVR screening using the domestic first-generation device, that is, the Venus A-Valve (Venus MedTech Inc., Hangzhou, China),[2] under the frame of the China Aortic valve tRanscatheter Replacement registrY (No. ChiCTR2000038526). The largest tertiary centers in a local region usually adopt a particular technique at first and then become widely used where the majority of local patients with relevant diseases being admitted to or referred to. The Venus A-Valve is the first commercially approved transcatheter aortic valve in China that now holds the largest market share. Thus, patients being sent to Venus' core laboratory can be considered as representative. All patients provided consent for anonymized data acquisition and analysis. The registry was approved by institutional ethical committees (Approval No.2019-975).

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Bicuspid aortic valve (BAV) morphologies were classified according to the Sievers system in the analytic reports we collected. In certain cases, "functional BAV" was recorded when fusion was not seen in the basal third of the sinus but occurred at or close to the commissural level.[3] Such patients represent the "partial-fusion type" in a recent consensus statement on nomenclature and classification of BAV[4] and thus was grouped as BAV patients and referred to as "partial-fusion BAV" in following analyses. The angulation between the plane of aortic annulus and a horizontal reference line >60° was regarded as horizontal aorta. The ellipticity was determined as (1 − minimum diameter/maximum diameter) × 100%. Measurements and statistical considerations are provided in Supplementary Methods, http://links.lww.com/CM9/A846. A literature review was also done on the previous reports delineating aortic root dimensions from different geographical backgrounds.

A total of 2097 patients were included. The mean age was 73.2 ± 7.6 years, and 58.4% (1225/2097) of patients were male. Patients from Northern China were the most elderly. BAV morphology accounted for 54.0% (1133/2097) of the cohort with a proportion of type 0, type 1, type 2, and partial-fusion BAV of 42.5% (482/1133), 34.6% (392/1133), 1.8% (20/1133), 20.6% (233/1133), respectively (0.5% [6/1133] of patients were categorized as BAV but not subclassified in the database). Quadricuspid aortic valve was identified in 0.2% (5/2097) of the cohort. The highest proportion of BAV cases was seen in Central China (63.4%[123/194]) and the lowest seen in Northern China (45.8% [251/548]; Figure 1). The perimeter of aortic annulus was smaller than the lower bound of the sizing chart of Venus A-Valve (53 mm) in 0.1% (2/1822) of patients and greater than the upper bound (91 mm) in 7.4% (135/1822) of patients. The mean volume of calcification within the aortic root was 550.2 mm^3 whereas a total of 15.4% (288/1874) and 22.3% (417/1874) of patients had a volume of calcification exceeding 1000 mm^3 and <150 mm^3, respectively [Supplementary Figure 1, http://links.lww.com/CM9/A846]. The height of either coronary ostia was <10 mm in 14.2% (265/1862) of patients. A horizontal aorta was identified in 23.3% (422/1811) of patients. In patients being planned for transfemoral TAVR, 23.6% (276/1172) of patients had a diameter of <6 mm of the main access.

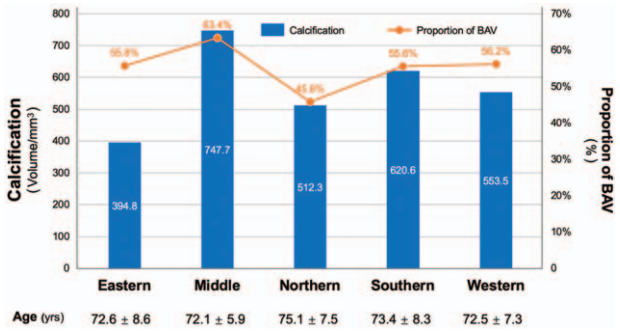

Figure 1: Geographical distribution of aortic root calcification burden and bicuspid morphology of TAVR candidates in China. TAVR: Transcatheter aortic valve replacement.

BAV patients had a relatively larger aortic annulus than patients with tricuspid morphology (Supplementary Table 1, http://links.lww.com/CM9/A846; area: 477.5 ± 112.7 mm^2 *vs.* 451.2 ± 177.9 mm^2, $P < 0.001$), but the shape of annulus was less elliptical in BAV (eccentricity: 21.7 ± 8.4% *vs.* 23.1 ± 7.0%, $P < 0.001$). The calcification burden was heavier in BAV patients (558.7 [269.4–932.5] mm^3 *vs.* 263.3 [95.9–536.7] mm^3, $P < 0.001$). In comparisons between definitely subclassified type 1 and type 0 bicuspid patients, type 0 morphology had a smaller aortic annulus (Supplementary Table 1, http://links.lww.com/CM9/A846; perimeter: 75.98 ± 9.10 mm *vs.* 80.60 ± 8.90 mm, $P < 0.001$) but a less elliptical aortic annulus (eccentricity: 19.9 ± 9.2% *vs.* 23.2 ± 7.6%, $P < 0.001$). The volume of calcification was less in type 0 than type 1 (576.0 [298.6–943.8] mm^3 *vs.* 641.7 [313.1–1008.9] mm^3, $P < 0.001$).

Patients from Northern China demonstrated the smallest anatomy at the annular, sinus and sinotubular junction (STJ) level, whereas patients from Western China had the most dilated ascending aorta [Supplementary Table 2, http://links.lww.com/CM9/A846]. Calcification burden was the heaviest in patients from Central China and the lightest in patients from Eastern China (583.0 [203.4–1180.0] mm^3 *vs.* 239.3 [67.9–560.0] mm^3; Figure 1). A total of seven studies were summarized in Supplementary Table 3, http://links.lww.com/CM9/A846 as comparisons of our results. Type 0 BAV was more commonly seen in Chinese BAV patients (~40% *vs.* ~12%). The volume of aortic leaflet calcification in BAV was higher in Chinese patients (~680 mm^3 *vs.* ~350 mm^3).

The current study represents the largest cohort to date of Chinese patients with symptomatic severe aortic stenosis being screened for TAVR. The major findings are (a) at a mean age of 73 years, the proportion of BAV morphology in this cohort was 54%, higher than similar registries of more elderly patients in industrialized countries. (b) Type 0 subtype accounted for over 40% of BAV in China, different from the type 1 dominance seen in other registries. (c) The volume of aortic leaflet calcification was higher in Chinese patients. (d) BAV patients had a relatively larger anatomy and higher calcification volume than tricuspid aortic valve, but their annulus was less elliptical in the current cohort. (e) Type 0 subtype had a smaller but less elliptical aortic annulus and less calcification than type 1 subtype. (f) Regional differences exist in aortic root dimensions and calcification burden in China. Given these features, international trials should consider enrollment in Chinese centers to cover a broader range of TAVR patients, and the Chinese community might benefit from an adapted TAVR strategy in face of our anatomical distinctions.

The high proportion of BAV cases seen in China has now largely been attributed to the younger age of patients. However, around threefold higher proportion of type 0 morphology in BAV cases seen in China suggests a possibility of intrinsic variance (eg, genetic factors). Although Asian patients have been reported to have less type 0 BAV than European patients in a previous multicenter study,[1] the difference in imaging modality (ie, MSCT *vs.* echocardiography) and targeting patient population (ie, being evaluated for TAVR *vs.* echocardiography-diagnosed

BAV) as well as the study design not involving Chinese centers should be considered when interpreting this study and ours. Type 0 BAV poses some additional problems to TAVR procedure, such as the difficulty in determining the virtual annulus with only two hingepoints and a higher rate of mean transprosthetic gradient ≥20 mmHg than type 1 patients.[5] The roughly twofold calcium burden in both bicuspid and tricuspid morphologies in China is also alarming since aortic root calcification has been identified as a risk factor for paravalvular leak, pacemaker implantation, and device success.[6] Some Chinese domestic devices have increased radial force of the stent frame to achieve optimal valve expansion in such settings.[7] Whether it may bring clinical benefits comparing with devices of higher conformability, along with a tailored treatment strategy and device design taking characteristics of Chinese patients into consideration, warrants further research studies. Balloon-expandable devices, on the other hand, provide greater opening force to secure circular expansion and minimize paravalvular leak but may be associated with higher risk of annular rupture.

The great geographical and climatic diversity, as well as regional variances of socioeconomic patterns, ethnic groups, and lifestyle likely produce anatomical differences of the aortic root across China. The observed smaller anatomy in the northern subgroup might be attributed to the lower proportion of BAV cases due to their elder age. Nonetheless, it is interesting to notice a nearly twofold higher volume of calcification in the central than the eastern subgroup. Aortic valve calcification is a multi-facet process and is frequent with aging and atherosclerotic risk factors, such as diabetes, hypertension, and higher body mass index.[8] Although the current study lacks means to delineate the underlying reason for this regional difference, it will be a noteworthy epidemiological topic.

One particular challenge when conducting this analysis was classifying the morphology of three commissures where two are normal and the third is fused <50%. The most widely used system came from surgical specimens, thus having inherent mismatches by determining the morphology through MSCT. A TAVR-directed classification based on leaflet morphologies and orientation has been formulated, where the bicommissural raphe and non-raphe types represent Sievers type 1 and type 0 BAV and the tricommissural subtype is conventionally referred to as "functional" or "acquired" BAV. The tricommissural entity was associated with a possible excess of new pacemaker implantation after TAVR than a true tricuspid aortic valve.[3] The pitfall of misclassification of aortic valve morphology still exists in contemporary studies, which impacts the interpretations of different studies.

The study is limited by the retrospective design with possible selection bias of enrolled patients and participating centers. Only MSCT data were collected for this analysis; thus, the imaging findings were not grouped by different grade of complicating aortic regurgitation or correlated with clinical outcomes. The core laboratory did not follow each site's clinical decisions; thus, a rejection rate for TAVR in these patients after the anatomy being evaluated could not be derived. Errors may exist in subclassifying "partial-fusion BAV." The fusion pattern of type 1 BAV was not recorded in the original database, leading to a lack of information in the current report.

Chinese patients being sent for TAVR screening have certain anatomical distinctions including but not limited to a more prevalent type 0 BAV morphology and a higher burden of calcification than other countries. Regional differences in aortic root anatomy are also observed within China. Such characteristics are of clinical implication when interpreting studies reporting TAVR outcomes from different countries.

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Conflicts of interest

Dr. Yuan Feng and Dr. Mao Chen are proctors/consultants of Venus MedTech, MicroPort, and Peijia Medical. The other authors report no disclosures.

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