To the Editor: Coronary artery aneurysms (CAAs), one of the complications of Kawasaki disease (KD), can cause myocardial ischemia, infarction, and even sudden death.[1] Accurate thrombotic risk stratification in KD patients with CAAs is critical in determining whether patients need aggressive anticoagulation therapy.

In recent years, computational fluid dynamics (CFD) has shown that hemodynamic parameters, such as low wall shear stress (WSS), can assist in the management of cardiovascular diseases. Some studies have attempted to determine the hemodynamic and morphological characteristics of thrombosed CAAs. These works have primarily focused on the advantages of hemodynamics or the thrombotic prediction by multidimensional morphological parameters.[2] Up to now, there is still no study that demonstrates a thrombotic risk score in combination with morphology- and hemodynamics-based parameters for CAAs in KD patients. Therefore, the goal of this study was to find significant morphological and hemodynamic parameters that may correlate with CAA thrombosis.

The Ethical Review Committee of the West China Hospital of Sichuan University (Chengdu, Sichuan, China) approved this study. It was conducted in accordance with the principles stipulated by the Declaration of Helsinki and meets the requirement of medical ethics. Written informed consent was not required for this study because it was a retrospective and observational study.

This retrospective and observational study included 48 CAAs from 29 KD patients who underwent computed tomography angiography (CTA) of coronary arteries at the West China Hospital of Sichuan University (Chengdu, Sichuan, China). All the CAAs were divided into a high-risk (n = 18) and low-risk group (n = 30) depending on the presence or absence of thrombosis, which was determined by CTA.

The patient-specific 3D coronary models were established from CTA image data using open-source software (Simvasuclar, simtk.org, 20.04.06),[3] and 35 parameters (Supplementary Table 1, http://links.lww.com/CM9/A876) were investigated. The typical aortic waveforms, Windkessel RCR boundary conditions, and lumped parameter network coronary models were applied at the aortic inlet, the aortic outlet, and coronary outlets, respectively (Supplementary Figure 1, http://links.lww.com/CM9/A876).[4] The resulting meshes had about 1.5 million unstructured tetrahedral elements. More details could be found in the literature and our previous work.[4,5]

All statistical analysis was performed using MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium). Each of the parameters was scaled to span a range from 1 to 3. The results were presented in 95% confidence intervals, and a P value of < 0.05 was defined a priori to be statistically significant.

Considering the differences between univariate parameters in the two groups, the proportion of female patients, right coronary artery CAAs, and the mean age was 22.22%, 72.22%, and 27.06 years in the high-risk group, whereas in the low-risk group they were 16.67%, 46.67%, and 32.47 ± 30.33 years, respectively. There were no significant differences in the three characteristics between the two groups (Supplementary Table 2, http://links.lww.com/CM9/A876). Additionally, the two groups had significant differences in most univariate morphological parameters and some of the univariate hemodynamic parameters (Supplementary Tables 3, http://links.lww.com/CM9/A876 and 4, http://links.lww.com/CM9/A876). These parameters included: Dclin (P = 0.0001), Dmax (P = 0.0001), RMD (P = 0.0012), Length (P = 0.025), Amax (P = 0.0005), RAla (P = 0.0047), the surface area of the aneurysm (SA) (P = 0.0003), V (P = 0.0018), undulation index (UI) (P < 0.0001), time...
average WSS (TAWSS) average \( P < 0.0001 \), oscillatory shear index (OSI) average \( P = 0.0089 \), relative residence time (RRT) average \( P = 0.0297 \), endothelial cell activation potential (ECAP) average \( P = 0.0073 \), OSI std\% \( P = 0.0055 \), ECAP std\% \( P = 0.0217 \), \( A_{(\text{TAWSS}<4)\%} \) \( P < 0.0001 \), \( A_{(\text{RRT}>4)\%} \) \( P = 0.0021 \), \( A_{(\text{ECAP}<0.05)\%} \) \( P = 0.0004 \), and normalized TAWSS (NTAWSS) \( P = 0.0003 \). However, there were no significant differences in RL/D \( P = 0.0914 \), non-sphericity index \( P = 0.6407 \), TAWSS min \( P = 0.18 \), TAWSS max \( P = 0.2077 \), OSI max \( P = 0.059 \), RRT max \( P = 0.7308 \), normalized relative residence time (NRRT) max \( P = 0.4116 \), ECAP max \( P = 0.0674 \), TAWSS std\% \( P = 0.9032 \), RRT std\% \( P = 0.3811 \), NRRT std\% \( P = 0.3009 \), \( A_{(\text{OSI}>0.2)\%} \) \( P = 0.0555 \), and \( A_{(\text{NRRT}>1)\%} \) \( P = 0.5 \). Furthermore, Figure 1A shows the hemodynamic parameter distribution contour maps on CAA vessel walls.

Regardless of the diameter, the areas of abnormal hemodynamic parameters in high-risk group aneurysms were large and concentrated, whereas in the low-risk group, they were small and scattered.

As suggested by the correlation coefficient \( r \) and the univariate regression analysis (Supplementary Table 5, http://links.lww.com/CM9/A876), \( D_{\text{clin}}, D_{\text{max}}, R_{\text{Di}}, A_{\text{max}}, R_{\text{Af}}, SA, V, UI, \text{TAWSS average}, A_{(\text{TAWSS}<4)\%}, \) and \( A_{(\text{RRT}>4)\%} \) were significantly correlated with the thrombosis. The largest ratio of the thrombosis of morphology and hemodynamics was 14.3254 and 5.0974 for each grade increase of \( V \) (and UI) and TAWSS average (and \( A_{(\text{TAWSS}<4)\%} \)), respectively. The area under the curve (AUC), the confidence interval, and the cutoff value of morphological and hemodynamic parameters were shown.

Figure 1: (A) Hemodynamic parameter distribution contour maps on vessel walls of coronary aneurysms. From left to right: TAWSS, OSI, RRT, NRRT, and ECAP. (B) The CRS of all aneurysms and the ROC curves of the MRS, HRS, and CRS. CRS: Combined risk score; ECAP: Endothelial cell activation potential; HRS: Hemodynamics risk score; MRS: Morphology risk score; NRRT: normalized relative residence time; OSI: Oscillatory shear index; ROC: Receiver operating characteristic; RRT: Relative residence time; TAWSS: Time average wall shear stress.
Based on the above, the sign suggested, CRS analysis indicated that multidimensional parameters (like TAWSSmin) were 8.2 (mm), 4.33 (dyne/cm²), 0.05, 63.51(%), and 9.31(%), respectively.

In accordance with the multivariate logistic regression analysis (Supplementary Table 6, http://links.lww.com/CM9/A876), five parameters, \( D_{\text{max}} \) (\( P = 0.0039 \)), TAWSSaverage (\( P = 0.0457 \)), OSIaverage (\( P = 0.0853 \)), ECAPaverage (\( P = 0.0147 \)), and \( A_{\text{RRT-4\%}} \) (\( P = 0.0478 \)), were identified as independent risk factors related to the thrombosis. If a CAA met the cutoff value, the risk factor was 1; otherwise, it was 0. The morphology risk score (MRS), hemodynamics risk score (HRS), and combined risk score (CRS) (MRS based on \( D_{\text{max}} \), HRS based on TAWSSaverage, OSIaverage, ECAPaverage and \( A_{\text{RRT-4\%}} \), and CRS based on all five risk factors) were obtained by adding risk numbers. In Figure 1B, CRS had the highest discriminating accuracy (AUC = 0.897, \( P < 0.0001 \)), in comparison with the HRS (AUC = 0.897, \( P < 0.0001 \)) and the MRS (AUC = 0.878, \( P < 0.0001 \)). Additionally, as the cutoff suggested, CRS > 2 was defined as a high risk.

Based on the above, the significant points of this study are as follows:

Firstly, in terms of morphology: (1) The univariate analysis indicated that multidimensional parameters (like \( A_{\text{max}} \), \( V \), and UI) were better than one-dimensional parameters (like \( D_{\text{max}} \) and \( R_{\text{LD}} \)); (2) A single morphological factor could not distinguish the aneurysms with or without thrombosis accurately; (3) The multivariate logistic regression analysis showed that there were strong correlations among morphological parameters; and (4) The \( D_{\text{max}} \) (cutoff 8.2 mm, \( P < 0.0001 \)) was the morphological risk factor for thrombosis.

Secondly, in terms of hemodynamics: (1) As a single factor, the “relative” parameters, such as \( A_{\text{TAWSS<4\%}} \) (AUC = 0.831, \( P < 0.0001 \)) could differentiate the high-risk from the low-risk group better than “absolute” parameters, like TAWSSmin (AUC = 0.73, \( P = 0.0026 \)), (2) Multiple hemodynamic parameters could complement each other and improve the accuracy of the thrombosis prediction. Four hemodynamic risk factors, TAWSSaverage, OSIaverage, ECAPaverage, and \( A_{\text{RRT<4\%}} \), described the magnitude of frictional force, the frequency of shear force direction change, the blood cell stagnation, and the concentration position of disorder, respectively, which are related to the inflammatory response and the thrombosis.[2]

Finally, we concluded that although the MRS (based on \( D_{\text{max}} \) and HRS (based on TAWSSaverage, OSIaverage, ECAPaverage and \( A_{\text{RRT<4\%}} \)) were clinically useful discriminants of the CAA thrombosis with high AUC values (0.83 and 0.89 respectively), the CRS (based on all five parameters) had the highest accuracy (AUC = 0.941, \( P < 0.0001 \)). The CRS implied a gradual process caused by the changes in the geometry and blood flow pattern of CAA and could provide theoretical support for doctors and potentially act as a clinical index for thrombotic risk stratification of CAA in KD patients.

In this study, we proposed a scoring system for thrombotic risk stratification in KD patients with CAA. We believed that this system (upon further improvement) was applicable in many situations and had reference value. To improve the system, a much larger cohort of patients is needed to improve and verify the parameters and values used in the CRS to make the output more statistically significant. The five risk factors were directly screened out by multiple logistic regression. Considering the number of samples, we did not exclude the OSI average (\( P = 0.0853 \)), which was expected to be improved. In addition, the CFD analysis could be optimized by incorporating the use of non-Newtonian fluids and the blood vessel wall elasticity. We hope to identify a combination of morphological and hemodynamic parameters that underpins thrombosis or even clinical outcomes in the future.

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Conflicts of interest

None.

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