In-vivo validation of a nomogram with isostiffness-lines for the assessment of aortic stenosis severity

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Background: In patients with low-flow, low-gradient aortic stenosis, the aortic valve opening area (AVA) projected at a higher standardized transvalvular flow (Q) is used to assess the severity of aortic stenosis. It assumes a linear relation between Q and AVA. We investigated whether a sigmoid function better captured this relation and whether a nomogram could be constructed.

Methods: We measured instantaneous AVA and Q in 142 patients with the whole spectrum of AS including very low-flow situation on one ejection cycle. We defined a linear and a sigmoid function containing hyperparameters as well as the relative stiffness. Using a k-fold cross validation algorithm, we first trained the hyperparameters of each function on the subgroup of patients with normal aortic valve. Using the obtained hyperparameters, we then fitted the relative stiffness for each of the patients with AS on the lowest 70%, 50%, 30% and 10% Q of the (Q:AVA) data points of the ejection cycle. We then assessed the accuracy of the two models by computing the mean squared error (MSE) of the predicted AVA vs the measured AVA on the remaining 30%, 50%, 70% and 90% data points and the Akaike Information Criterion (AIC). A receiver operating characteristic (ROC) analysis with computation of its area under the curve (AUC) was performed on the entire range of possible threshold of the relative stiffness to discriminate between severe from non severe aortic stenosis.

Results: The sigmoid consistently better predicted the remaining 70%, 50%, 30% and 10% AVA than the linear model (MSE: 6.62e-6 vs 14.11e-6, 4.90e-6 vs 12.39e-6, 4.90e-6 vs 14.84e-6, 4.90e-6 vs 22.99e-6; AIC: -7933 vs -7428, -13341 vs -12328, -13341 vs -16990, -13341 vs -21031, respectively).

The first figure depicts the assessment of the AVA predicted with the linear (left panel) and sigmoid (right panel) model with Q of the 30% highest Q values with linear regression. The black line on the linear regression graphs represent the identity function (f(x) = x). The closer to this line are the points, the more accurate is the prediction.

In the ROC analysis, the calculated AUC was 0.88, performed on all patients with relative stiffness obtained on the first 70% Q of the (Q;AVA) data points. The most discriminative relative stiffness threshold was 1.51 with a corresponding accuracy of 0.85.

The second figure depicts a nomogram with mean and confidence interval of iso-stiffness lines for each severity with the following color code: group of normal aortic valve in green, group of mild aortic stenosis in blue, group of moderate aortic stenosis in orange and group of severe aortic stenosis in red. The iso-stiffness line with most discriminant relative stiffness computed on the group of patients with moderate and severe aortic stenosis is depicted in black.

Conclusion: This study allows to construct a nomogram to compare the stiffness of the aortic valve of any patient at any Q, simplifying the severity grading system of AS.
Accuracy of AVA prediction

**Prediction of AVAs with 30% highest Qs**

**Linear model**
- $r$: 0.888
- Slope: 1.044
- Intercept: 0.025
- $p$ value: <0.001
- MSE: $14.11 \times 10^{-6}$
- AIC: -7428

**Sigmoid model**
- $r$: 0.923
- Slope: 0.923
- Intercept: 0.007
- $p$ value: <0.001
- MSE: $6.62 \times 10^{-6}$
- AIC: -7933

Accuracy of AVA prediction
Nomogram with iso-stiffness lines