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# A model based on clinical parameters to identify myocardial late gadolinium enhancement by magnetic resonance in patients with aortic stenosis: An observational study

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## Abstract

**Objective:** With increasing age, the prevalence of aortic stenosis grows exponentially, increasing left heart pressures and potentially leading to myocardial hypertrophy, myocardial fibrosis and adverse outcomes. To identify patients who are at greatest risk, an outpatient model for risk stratification would be of value to better direct patient imaging, frequency of monitoring and expeditious management of aortic stenosis with possible earlier surgical intervention. In this study, a relatively simple model is proposed to identify myocardial fibrosis in patients with a diagnosis of moderate or severe aortic stenosis.
**Design:** Patients with moderate to severe aortic stenosis were enrolled into the study; patient characteristics, blood work, medications as well as transthoracic echocardiography and cardiovascular magnetic resonance were used to determine potential identifiers of myocardial fibrosis.
**Setting:** The Royal Brompton Hospital, London, UK
**Participants:** One hundred and thirteen patients in derivation cohort and 26 patients in validation cohort.
**Main outcome measures:** Identification of myocardial fibrosis.
**Results:** Three blood biomarkers (serum platelets, serum urea, N-terminal pro-B-type natriuretic peptide) and left ventricular ejection fraction were shown to be capable of identifying myocardial fibrosis. The model was validated in a separate cohort of 26 patients.
**Conclusions:** Although further external validation of the model is necessary prior to its use in clinical practice, the proposed clinical model may direct patient care with respect to earlier magnetic resonance imagining, frequency of monitoring and may help in risk stratification for surgical intervention for myocardial fibrosis in patients with aortic stenosis.

## Keywords

Aortic stenosis, biomarkers, clinical model, left ventricular ejection fraction, magnetic resonance, myocardial fibrosis

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## Introduction

Aortic stenosis is a common valvular pathology with a prevalence that increases exponentially with age.[1] The increased ventricular pressures associated with aortic stenosis lead to myocardial hypertrophy which over time may lead to myocardial fibrosis (MF) and heart failure.[2]

Myocardial fibrosis identified on histopathology gives good correlation with measurements on late gadolinium enhancement (LGE) cardiovascular magnetic

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resonance (CMR).[3] LGE measured on CMR is a predictor of heart failure and cardiovascular complications requiring hospitalizations and has been used to detect replacement MF.[4,5] Furthermore, left ventricular MF is associated with left atrial functional abnormalities,[6] advanced cardiac hypertrophy,[5] and importantly both its presence and total burden are independent predictors of mortality in aortic stenosis, confirming the utility of CMR for risk stratification.[7–9]

The only current treatment for aortic stenosis is aortic valve replacement (AVR). While AVR may lead to regression of myocardial hypertrophy, it does not lead to regression of focal fibrosis as measured by LGE,[10] but can halt progression. Detection of early fibrosis by LGE is therefore important to improve clinical outcomes and possibly help identify patients that need earlier treatment to limit progression of fibrosis and limit the mortality risk associated with it.[5,10] Nevertheless, due to limited resources and the variable accessibility to CMR, it is important to risk stratify patients for CMR given that scanning all patients with AS would not be feasible.

Predictors of MF have been previously investigated. However, markers such as lipoprotein(a),[11] serum sST2 (member of interleukin-1 receptor)[12] have not been found to be suitable for the prediction of MF.[11,12]

Electrocardiographic findings of lower voltage transmission[13] as well as fragmented QRS complexes[14] among patients with hypertrophic cardiomyopathy may identify MF; however, the myocardial tissue has to be sufficiently fibrosed for derangement of electrical conduction to be identified.

On the other hand, plasma levels of miRNA-21 were previously shown to be associated with MF.[15,16] In addition, the cardiac myosin-binding protein C, a marker for myocardial injury and fibrosis, was found to correlate with hypertrophy and fibrosis as measured by LGE and may provide future direction for investigation.[17] Early detection of fibrosis based on other blood tests may be of utility to identify patients with AS at higher risk of MF, warranting further multimodality imaging and possible intervention.[18]

The purpose of this investigation was to develop a clinical risk score that would allow for the identification of patients at risk of having any myocardial replacement fibrosis, defined as either non-infarct midwall fibrosis or subendocardial-infarction pattern fibrosis, as both of these are associated with worse prognosis in patients with aortic stenosis. The objective of the "Fibrosis Risk Score" is to risk stratify patients for further imaging and direct management.

## Methods

The study has been approved by the National Ethics Committee and the Institutional Review Board of Royal Brompton Hospital, London, UK and undertaken in accordance with the ethical standards detailed in the Declaration of Helsinki. Written consent was obtained from all patients. This work represents a sub-study of prospectively recruited patients in the CMR study (ClinicalTrials.gov Identifier: NCT00930735).

At the Royal Brompton Hospital, CMR is routinely recommended for all patients with significant AS (in practice moderate/severe) and where the clinical team requires further information regarding the severity of AS, left ventricular (LV) function or aortic dimensions, thus enabling recruitment of patients with CMR scans for the study.

The derivation cohort consisted of 113 consecutive patients with AS who underwent CMR between 2011 and 2014 and had LGE. Additionally, 26 further patients were recruited in 2015 and formed the validation cohort.

Patients with disseminated malignancy, severe aortic regurgitation, moderate or severe mitral regurgitation/stenosis, previous valve replacement operations, contraindications to CMR (including pacemaker and defibrillator implantation), and an estimated glomerular filtration rate (Cockcroft-Gault equation) of $<30$ ml/min were excluded.

### Data collection

Patient demographic characteristics and medical histories were collected from the patient and their hospital or community records and reviewed on the day of the CMR. Medical conditions and prescribed medications were recorded. The presence of coronary artery disease was defined as prior coronary revascularization or the presence of significant coronary artery stenosis: $>50\%$ lumen diameter narrowing of a vessel of 2 mm diameter or greater as assessed by invasive or computed tomography coronary angiography.

### Cardiovascular magnetic resonance

CMR was performed using a 1.5 T scanner (Sonata or Avanto, Siemens, Erlangen, Germany) and a standardised protocol as described previously.[11]

In brief, balanced steady state free precession (SSFP) at end-expiration was used to guide acquisition of a vertical long axis (VLA) cine for initial localizer images. From these, two, three and four chamber views cines were undertaken. Contiguous 10 mm short axis slices of the LV were then taken from base to apex. Following administration of gadolinium contrast agent (Gadovist, Schering AG, Berlin, Germany), inversion recovery-prepared spoiled gradient echo

images were acquired in standard long- and short-axis views to detect areas of LGE.

### Image analysis

Once all imagining data have been collected, for both the derivation and validation cohorts, image analysis was undertaken using a dedicated software (CMRtools, Cardiovascular Imaging Solutions, London, UK). The presence and pattern of LGE were assessed on anonymised images by two independent blinded expert observers (Level 3 Society for Cardiovascular Magnetic Resonance accreditation) and used to categorise each patient according to the presence or absence of myocardial fibrosis, and if present, whether it was midwall fibrosis or subendocardial-infarction pattern fibrosis. The primary analysis was based on the presence of any fibrosis (non-infarction midwall or subendocardial-infarction pattern). Reproducibility of CMR imagining parameters has been previously established at Royal Brompton Hospital.[19]

In addition, echo parameters including peak velocity, peak and mean gradients and derived aortic valve area parameters were recorded and used as possible variables in identifying myocardial fibrosis.

### Biomarker analysis

During the 2011–2014 (derivation cohort) and 2015 (validation cohort) time periods, blood samples were collected on the same day as the CMR and stored. Biomarker analysis was undertaken in the accredited biochemistry laboratory at Royal Brompton Hospital upon completion of the recruitment to both studies.

Given that the lab defined urea as abnormal at values $\geq 7.5$ mmol/L, and NT-Pro BNP defined at levels $\geq 450$ pg/mL; these variables were reported in a dichotomous manner for statistical analysis. The biomarker data for the derivation and validation cohorts were statistically analysed at the same time.

### Statistical analysis

For baseline patient characteristics, continuous variables are presented as mean $\pm$ standard deviation (SD), and categorical variables are presented as absolute numbers and percentages. Mann–Whitney-Wilcoxon test were used for continuous variables and Fisher exact test for categorical variables for baseline characteristics among fibrosis and no fibrosis patient groups. Analysis was performed using Stata 15.1 (College Station, Texas, USA).

All variables were first included in univariable logistic regression models and these were used to assess the best functional form for continuous variables (linear scale, log scale, or binary cut-off). Univariate and multivariable Cox models were generated, and forward stepwise selection was used to find the optimal logistic regression model to predict fibrosis from all of the potential predictors. This multivariable model was used to assign predicted probabilities of fibrosis to each patient and verified using the Hosmer–Lemeshow goodness-of-fit test and the receiver operator curve (ROC) statistic. The model was firstly internally validated using a bootstrap method. Secondly, the model was used to predict the presence of any fibrosis for each patient in the validation cohort and assessed how the prediction related to the CMR scan findings.

## Results

All the patients who provided their consent and met the inclusion criteria were included in the study, there were no further exclusions. Overall, 113 patients with moderate or severe AS (mean age $76 \pm 10$; 69% male) underwent CMR imaging to determine the presence of midwall fibrosis or infarction as shown in Supplemental Figure 1. Baseline patient characteristics and variables investigated are shown in Supplemental Table 1 and Supplemental Text.

Thirty-seven patients (32.7%) showed no evidence of fibrosis. Seventy-six (67.3%) patients had fibrosis, 40 of which had midwall fibrosis and 36 had subendocardial-infarction pattern fibrosis. Eighty-five variables based on patient demographics, biomarker results, echocardiography and CMR parameters were assessed (variables with $p < 0.2$ included in Table 1).

Variables with $p \leq 0.2$ on the univariable analysis results were subsequently used in the multivariable logistic regression models with forward stepwise selection for the computation of the most favourable logistic regression model in identifying fibrosis.

In a multivariable model, platelet count, urea, LVEF and NT-Pro BNP remained the only significant variables ($p < 0.05$) (Table 2).

The final multivariable model, based on logistic regression model, was used to estimate the predicted probability of fibrosis to each patient. This was based on the three biomarkers and the LVEF as follows:

$$\text{Probability of Fibrosis} = \text{expit}\left(911.31 \times 0.84^{\frac{P}{10}} \times 4.03^{U} \times 0.94^{L} \times 3.75^{N}\right)$$

where $P$ is the number of platelets, $U$ is 1 if Urea $\geq 7.5$ mmol/L and 0 otherwise, $L$ is the percentage LVEF, $N$ is 1 if NT-ProbBNP $\geq 450$ pg/mL and 0 otherwise, and expit is the function where $\text{expit}(x) = \frac{x}{1+x}$.

**Table 1.** Univariate identifiers of fibrosis.

| Variable | Odds ratio | 95% confidence interval | | p value |
|---|---|---|---|---|
| NT-Pro BNP (≥450 pg/mL) | 7.15 | 2.81 | 18.20 | <0.001 |
| BNP (per log pg/mL) | 2.16 | 1.32 | 3.55 | <0.001 |
| LV EF (per 1%) | 0.95 | 0.92 | 0.98 | 0.002 |
| Platelets (per 10) | 0.89 | 0.82 | 0.97 | 0.007 |
| Age (per 10 years) | 1.64 | 1.10 | 2.43 | 0.015 |
| LV ESV (per 10) | 1.12 | 1.02 | 1.23 | 0.016 |
| Urea (≥7.5 mmol/L) | 3.15 | 1.24 | 8.00 | 0.016 |
| Euroscore II (per 1) | 1.28 | 1.04 | 1.57 | 0.018 |
| LA Volume (per 100 mm) | 3.03 | 1.21 | 7.58 | 0.018 |
| OPG (per log pmol/L) | 3.20 | 1.17 | 8.80 | 0.024 |
| Bilirubin (per μmol/L) | 1.11 | 1.01 | 1.22 | 0.028 |
| LA vol indexed (per 100 mL) | 6.09 | 1.16 | 31.88 | 0.033 |
| LA area 4Ch (per 100 mm) | 1.06 | 1.00 | 1.12 | 0.034 |
| BMI (per kg/m$^2$) | 0.92 | 0.84 | 1.00 | 0.053 |
| OPN (per log ng/mL) | 2.81 | 0.99 | 7.98 | 0.053 |
| Albumin (per g/L) | 0.89 | 0.79 | 1.00 | 0.055 |
| LV EDV (per 10) | 1.07 | 1.00 | 1.15 | 0.057 |
| Creatinine (per 10 μmol/L) | 1.16 | 0.99 | 1.35 | 0.062 |
| Sodium (per mmol/L) | 0.89 | 0.78 | 1.01 | 0.069 |
| LV mass (per 10 g/m$^2$) | 1.08 | 0.99 | 1.17 | 0.081 |
| LA area 2Ch (per 100 mm) | 1.04 | 0.99 | 1.10 | 0.083 |
| Troponin I (per log μg/L) | 2.21 | 0.88 | 5.57 | 0.092 |
| Wall thickness (per mm) | 1.13 | 0.96 | 1.34 | 0.14 |
| Echo PG (per 10) | 0.90 | 0.79 | 1.04 | 0.15 |
| Echo MG (per 10) | 0.86 | 0.70 | 1.07 | 0.17 |

Note: The table shows the variables associated with the presence of any fibrosis. Variables with $p \leq 0.2$ on the univariable analysis results, which were subsequently used in the derivation of the model, are reported from the total of 85 variables used.

**Table 2.** Multivariable identifiers of fibrosis.

| Variable | Odds ratio | 95% confidence interval | | p value |
|---|---|---|---|---|
| Platelets (per 10) | 0.84 | 0.75 | 0.94 | 0.002 |
| Urea (≥7.5 mmol/L) | 4.03 | 1.24 | 13.15 | 0.021 |
| LV EF (per %) | 0.94 | 0.89 | 0.99 | 0.023 |
| NT Pro BNP (≥450 pg/mL) | 3.75 | 1.06 | 13.34 | 0.041 |

Note: In a multivariable model, platelets, urea, LVEF and NT-Pro BNP were associated with midwall and subendocardial-infarction pattern type fibrosis.

A histogram of these probabilities is shown in Figure 1.

Depending on the clinical setting, the model allows for variable cut-off values to adjust sensitivity and specificity according to clinical requirements. For example, a probability cut-off of 0.50 will give 90% sensitivity of identifying fibrosis with 55% specificity, whereas a cut-off value of 0.90 will give 50% sensitivity with a specificity of 93%.

## *Internal validation*

A Hosmer–Lemeshow goodness-of-fit test indicated acceptable calibration of the model ($p = 0.44$). The AUC from the receiver operating characteristic (ROC) was 0.86, suggesting good discrimination. A bootstrap method was used to internally validate the discrimination of the model and the bias was estimated to be 3.9% (95% confidence interval (CI) 0.2%–9.9%) suggesting only a small amount of bias.

## *External validation*

In the validation cohort, the percentage risk of fibrosis divided into four groups, (Table 3) correlated well with the true presence or absence of fibrosis based on CMR (area under ROC curve 0.73). However, in view of the small number of patients, the confidence interval was relatively large (95% CI 0.50–0.97). Nonetheless, this

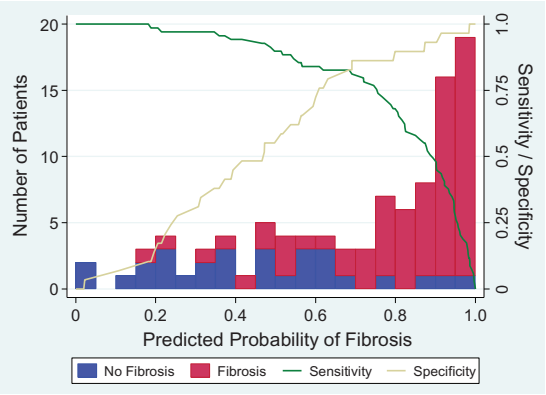


**Figure 1.** Histogram of the probability of fibrosis. The model is based on the platelet count, urea level, NT-Pro BNP level and left ventricular ejection fraction (LVEF), from which the probability of any fibrosis can be calculated for each patient. The sensitivity is shown in green and the specificity in golden-brown. The red bar represents patients who had fibrosis on CMR, and the blue bar represents patients who did not have fibrosis.

**Table 3.** Fibrosis risk prediction. How the fibrosis risk predicted was associated with the true presence or absence of fibrosis.

| Predicted risk % | Total number of patients | Patients with fibrosis (%) |
|---|---|---|
| 0–25 | 2 | 0 (0) |
| 25–50 | 1 | 1 (100) |
| 50–75 | 6 | 4 (67) |
| 75–100 | 17 | 15 (88) |

process supported the findings of the internal validation.

## Discussion

Using a large cohort of patients with AS who had undergone CMR to determine myocardial fibrosis, our team has developed and validated a risk score for fibrosis based on simple imaging and biomarker parameters.

Of the final variables that were computed into the Risk of Fibrosis Equation, some have been previously implicated in cardiovascular pathologies. NT pro-BNP, for example, has been previously reported to be a strong predictor of cardiovascular mortality[20] and was identified as the most important variable in predicting cardiovascular death in patients with stable coronary heart disease.[21] In AS patients, the biomarker was linked to disease severity and was proposed to be of use for post-surgical follow-up.[22,23] It should be noted, however, that aside from the myocardial fibrosis, a number of additional pre-disposing factors as well as confounders may be further correlated with biomarker expression, such as pressure overload, disease severity, cardiomyocyte hypertrophy, among others.[24,25]

Current guidelines recommend intervention to relieve aortic stenosis in the presence of symptoms or LVEF <50%.[26,27] However, these guidelines are potentially limited because they allow patients to decompensate before they are eligible for intervention; subsequently, patients may have a poorer response to treatment. Therefore, appropriate use of CMR to identify earlier signs of decompensation, including fibrosis, might enable better monitoring and appropriate intervention for such patients.[28] CMR represents an excellent imaging modality for such patients as it is safe and radiation-free and also gives information on the valve (gradient, anatomy, valve area), the aorta (size, coarctation) and the myocardium (LV and RV function, left atrial (LA) size, myocardial thickness and fibrosis). However, not all patients can undergo CMR and, crucially, its use is limited by clinical availability in many parts of the country and indeed the world. Therefore, a simple risk score to identify fibrosis is an important step as it has two potential uses.

The score can be used to streamline the use of CMR with LGE in patients with AS. The flexibility and versatility of the model allow it to be modified to support different clinical environments and needs. For example, where CMR is easy to obtain, a low cut-off value of fibrosis risk (e.g. 20%) could be used to allow increased sensitivity (95% in this case), whereas when CMR is difficult to access, a high cut-off (e.g. 90%) will allow high specificity (93%). Furthermore, even if the patients do undergo CMR, if the need for gadolinium is negated (by correctly estimating the presence/absence of fibrosis in advance), then the duration of the scan could be quicker and not require intravenous cannulation or contrast administration, which can reduce both the time of the scan and the cost.

This model has the potential to be used as a serial early marker of decompensation, allowing annual monitoring of patients with asymptomatic AS. Once the percentage risk increases, it would be suggestive of decompensation and CMR can be arranged and the patient potentially considered for surgery. However, this will need to be fully validated in a prospective study.

### *Study limitations*

Although the model is designed to "identify" the presence of myocardial fibrosis, we cannot comment on the potential impact on management and subsequent intervention and whether this can improve outcomes.

Although it would be logical to assume this given the evidence of worse outcome in the patients with fibrosis,[8,28] this needs to be confirmed either in a prospective study or retrospectively in multi-centre work where both CMR and biomarker parameters are available from the time of the CMR. The midwall and infarction fibrosis groups were merged in order to provide adequate power; however, a separate model for each of these pathologies might have better sensitivity and specificity. Nonetheless, both midwall and infarction fibrosis have similarly adverse prognosis justifying using a combined approach.[9] LGE has been utilized in the past for the assessment of mid-wall fibrosis and subendocardial delayed enhancement.[29] Our study focused on LGE imagining to identify myocardial fibrosis in a dichotomous (present/absent) manner. In the future, assessing the validity of the model to identify graded severity of myocardial fibrosis as identified by LGE or utility of other imagining modalities such as T1 mapping may be of benefit. In addition, although our model has shown strong internal validation and good external association from a separate small cohort in our institution, we did not have large external validation from a separate institution which is the gold standard for any risk model. Furthermore, this work was carried out in a single institution with a predominantly Caucasian patient population, therefore it remains to be seen if it would be applicable in other populations. Also, the potential effect of medication use on the final four variables within the fibrosis identification model has not been evaluated in our study and may have played an effect on the results, although such an effect would have weakened the associations seen. As such we believe that the medication use did not influence the conclusion of our paper. Finally, our troponin assays have a lower limit of detection as 18 ng/L, whereas more modern assays have thresholds as low as 1.2 ng/L,[30] therefore potentially reducing its effect.

## Conclusions

We have developed, internally validated and externally confirmed a flexible fibrosis risk model in aortic stenosis which could be used in clinical practice to reduce the need for CMR, but also for serial monitoring and identifying patients at risk of early decompensation. The model is versatile and can be adjusted according to the clinical need. Prior to full implementation in clinical practice, however, a full external validation and investigation into the association of this model with longer-term clinical outcomes is required.

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### Contributorship

VSV conceived the idea designed the study, analysed data and co-wrote the first draft. MK co-wrote the first draft and analysed data. SN undertook statistical analysis. FA analysed data. MD, DJP, SK designed the study and provided funding. All authors edited the first draft and approved the final version of the manuscript.

### Declarations of conflicting interests

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### Ethical approval

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### Supplemental material

Supplemental material for this article is available online.

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