Establishment and Validation of a Predictive Model for Long-Term Severe Functional Tricuspid Regurgitation after Mitral Valve Replacement

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ABSTRACT

Background: The objective was to develop and validate an individualized nomogram to predict severe functional tricuspid regurgitation (S-FTR) after mitral valve replacement (MVR) via retrospective analysis of rheumatic heart disease (RHD) patients’ pre-clinical characteristics.

Methods: Between 2001-2015, 442 MVR patients of RHD were examined. Transthoracic echocardiography detected S-FTR, and logistic regression model analyzed its independent predictors. R software established a nomogram prediction model, and Bootstrap determined its theoretical probability, which subsequently was compared with the actual patient probability to calculate the area under the curve (AUC) and calibration plots. Decision curve analysis (DCA) identified its clinical utility.

Results: Ninety-six patients developed S-FTR during the follow-up period. Both univariable and multivariate analyses found significant correlations between S-FTR occurrence with gender, age, atrial fibrillation (AF), pulmonary arterial hypertension (PH), left atrial diameter (LAD), and tricuspid regurgitation area (TRA). The individualized nomogram model had the AUC of 0.99 in internal verification. Calibration test indicated high agreement of predicted and actual S-FTR onset. DCA also showed that utilization of those six aforementioned factors was clinically useful.

Conclusion: The nomogram for the patient characteristics of age, gender, AF, PH, LAD, and TRA found that they were highly predictive for future S-FTR onset within 5 years. This predictive ability therefore allows clinicians to optimize postoperative patient care and avoid unnecessary tricuspid valve surgeries.

INTRODUCTION

Tricuspid regurgitation (TR) refers to blood flow reversal from the right ventricle (RV) into the right atrium via the tricuspid orifice, during systole. It is classified into primary and secondary types, where the former results from inherent valvular disease, while the latter does not involve any valvular abnormalities. Secondary, also known as functional TR (STR/ FTR), is a common occurrence post mitral valve replacement (MVR) surgery of rheumatic heart disease (RHD), and often is aggravated post-operation, leading to irreversible RV dysfunction, heart failure, and death [Topolsky 2019; Gao 2020; Wang 2019]. As a result, the 2020 American Heart Association/American College of Cardiology guidelines recommend severe FTR (S-FTR) patients to simultaneously undergo MVR and tricuspid valve (TV) surgery. However, whether mild/moderate FTR patients should also undertake these procedures remains controversial [Otto 2021]. Therefore, a wide gap remains between recommended guidelines and actual practice, and essential therapeutic questions remain unanswered, such as optimal prophylactic TV repair (TVr) timing and identifying likely surgery beneficiaries for improving quality of life. It is still challenging to decide whether to perform isolated TV surgery, due to limited data availability for guiding preoperative assessments, as well as procedural optimization. However, increasing evidence suggests that FTR does not always improve post MVR surgery in some patients, resulting in high mortality and poor long-term prognosis [Wang 2019]. By contrast, multiple investigators have found that prophylactic TV surgery during MVR improves this long-term prognosis [Dreyfus 2018; Pozzoli 2017], though other researchers dispute this, arguing that increased surgical risk outweighs any cardiac functional improvements [Vassileva 2014]. This disagreement leads to TV surgical repair procedures being underutilized, with preventative TVr decision-making, especially for mild FTR, still mainly being based on the surgeon’s personal experience. Therefore, to avoid any unnecessary TV surgery and ensure timely interventions for S-FTR patients to improve their long-term postoperative prognoses, careful preoperative assessment is crucial for patients being considered for TVr. However, none of the risk factors alone serve as accurate and specific criteria for S-FTR recurrence/aggravation [Topolsky 2019; Kusajima 2016; Vaturi 2016]. Currently, no predictive S-FTR occurrence model, post MVR, exists.
We remedied this omission in this study by developing such a model using a nomogram. Nomogram can quantify individualized clinical event risks through simple graphics, providing individualized treatment guidance [Yang 2020]. From this study, the nomogram for the aforementioned S-FTR risk factors: age, gender, left atrial diameter (LAD), pulmonary arterial hypertension (PH), atrial fibrillation (AF), and tricuspid regurgitation area (TRA) collectively were able to predict its onset within 5 years post MVR, providing additional guidance to determine optimal post-surgery follow up, such as whether to perform TVr.

**MATERIALS AND METHODS**

**Study cohort:** A total of 813 consecutive adult patients of RHD, who underwent MVR between January 1, 2001-December 31, 2015, were considered for study inclusion. The patients’ cardiologists and cardiac surgeons individually made the decision to undergo either surgical intervention or medical management. For study inclusion, patients of RHD must have met the following criteria: 1) ≥18 years, 2) mild/moderate FTR, 3) MVR conducted by the first cardiac surgeon visited, and 4) available complete data. Criteria for patient exclusion were: 1) existing congenital heart disease, myocardiopathies, infective endocarditis, or organic TV disease with inadequate pulmonary artery systemic pressure (PASP), 2) no additional cardiac surgery received during the follow-up period, and 3) incomplete follow-up data. Based on these criteria, the study ultimately examined 442 patients. (Figure 1)

**Data collection:** The retrospective study was conducted in accordance with the Declaration of Helsinki ethical standards and was approved by the ethics committee. The informed consent requirement was waived. Privacy and personally identifiable information for all patients were protected. Hospital Information System (HIS) was used for data collection. To prevent “over-fitting” of the resulting predictive model, the S-FTR predictive factor questionnaire used in this study was designed based on previous literature and expert opinions on S-FTR risk factors. The questionnaire included the following queries: 1) Basic information of patients undergoing MVR, including gender and age, 2) Parameters measured for each patient by transthoracic echocardiography (TTE), including LAD, right atrial transverse (RATD) and longitudinal diameters (RALD), left ventricular end diastolic diameter (LVEDD), mitral and tricuspid regurgitation areas (MRA and TRA), AF and PH. All measurements were obtained from the last ultrasound report before surgery and were evaluated in accordance with internationally recommended standards TTEs [Lang 2015]. PASP was calculated by adding RA pressure, estimated by assessing inferior vena cava size and collapsibility, to the peak systolic gradient of the TR signal by continuous-wave spectral Doppler [Lang 2015].

**Follow up and possible patient outcomes:** Pre-discharge, general patient information, such as gender, age, cardiac function, as well as surgery date and type, were recorded. Regularly scheduled echocardiography was performed as

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**Figure 1.** Flowchart for patient of rheumatic heart disease (RHD) inclusion in the retrospective analysis. After applying exclusion criteria (congenital heart disease, follow-up loss, organic thoracic regurgitation (TR) history, heart valve surgery during follow-up period), 442 patients were included.

**Figure 2.** Nomogram for the predictive severe functional tricuspid regurgitation (S-FTR) model. Five-year S-FTR free probabilities are predicted through identifying patient values for each variable (sex, age, AF, PH, TRA, and LAD) and summing up their associated points values to obtain Total Points that corresponds with a specific 5-year, S-FTR-free probability axis value. AF, atrial fibrillation; PH, pulmonary arterial hypertension; TRA, tricuspid regurgitation area; LAD, left atrial diameter.
follow up post-discharge, along with consulting hospital and outpatient medical records and filling in the aforementioned S-FTR predictive factor questionnaire. Echocardiography data was obtained from the echocardiography reports within the ultrasound database. The study endpoint was determined to be post-operation S-FTR onset within ≤60 months. According to the guideline, FTR was quantified using the proximal isovelocity surface area (PISA) method. we graded FTR in an integrated manner as mild, moderate, or severe [Zoghbi 2017]. Additionally, TV surgery (TVr /replacement) execution after MVR was simultaneously recorded.

Statistical analysis and establishing the predictive model: SPSS (version 20.0) and R (version 3.5.2) software performed all statistical analysis. Median and mean values for all variables were obtained with appropriate ranges, standard deviations, and percentages. An individualized nomogram, based on both univariate and multivariate event analysis results from the logistic regression model, was obtained with the regression coefficient for each predictor in the nomogram determining its weight. The linearity and proportionality assumptions were all verified by R software, in which the former was tested using Martingale residuals and the latter by using scaled Schoenfeld residuals. Odd ratios (OR) and their corresponding 95% confidence interval (95%CI) for each variable were calculated. The nomogram model was internally verified by Bootstrap, entailing 1000 repetitions of sample corrections within the modeling group, and degree of discrimination was calculated by the receiver operating characteristic (ROC) curves to calculate the area under the curve (AUC). The predictive model accuracy was further verified through establishing a calibration plot between predicted and actual S-FTR incidence rates, in which a better plot (closer matches between rates) indicates higher accuracy. To determine whether better clinical care decisions could be made with the predictive nomogram model for detecting and treating S-FTR post MVR than without and thus its clinical applicability, decision-curve analysis (DCA) was used [Steyerberg 2014]. All aspects of predictive model establishment, verification, evaluation, and reporting were carried out based on Transparent Reporting of a multivariate prediction model for Individual Prognosis or Diagnosis statement [Collins 2015]. All of them were two-sided, and $P < 0.05$ was considered statistically significant.

### RESULTS

**Characteristics of patients:** Out of the 442 RHD patients analyzed, 281 (63.6%) were female, and mean age was 50.7 years. Postoperative follow-up duration was 56.2±9.20 months, and 21.7% of cases developed S-FTR. No patients received TV surgery within the 5-year period. Table 1 shows preoperative clinical characteristics for all patients. (Table 1)

**Establishing a predictive model for S-FTR after MVR:** Statistically significant variables found in the univariate analysis were included in the multivariate logistic regression analysis, where the backward elimination method was used, followed by the regression coefficient test to select the maximum likelihood ratio statistic. This process discovered six independent risk factors: gender, age, AF, PH, LAD, and TRA. Each risk factor's OR was calculated, and all six were included in the predictive model. (Table 2) To determine their effectiveness for predicting S-FTR post MVR, a nomogram for scoring S-FTR risk was constructed. (Figure 2) Risk was scored as follows: An axis was drawn for each risk factor type on the nomogram, and specific values/classifications for each risk factor axes correspond to a specific point value on the Points axis. The resulting Total Points value (ranging 0-350) obtained by summing up these corresponding Points values, corresponds to a specific point on the 5-year S-FTR-free probability axis. For instance, a female 50-year-old RHD patient with AF, 45 mm LAD and 4.50 cm² TRA would have a Total Points value of 170, as age 50 = 45, female=28, AF=45, no PH=0, 45mm LAD=32, and 4.50cm² TRA=20 points (45+28+45+0+32+20). This value, in turn, corresponded with a 5-year S-FTR-free probability of >85%, and thus S-FTR onset within 5 years is <15%.

**Evaluation and validation of S-FTR nomogram prediction model:** Bootstrap internally verified the predictive...
nomogram model, entailing modeling group self-sampling, followed by discrimination and calibration evaluation. With respect to discrimination, the AUC was found to be as high as 0.99 (95% CI=0.98-0.99), indicating the model was highly capable of discriminating between S-FTR presence and absence. The model was then calibrated on a calibration curve, where X-axis represents its predicted probability for long-term S-FTR among patients undergoing MVR, and Y-axis the actual S-FTR occurrence. The curve showed that the cross-spot (solid black) line, representing nomogram model prediction-actual S-FTR occurrence correlation, closely corresponded to the dashed reference line (representing exact correlation), indicating the model was highly predictive (Figure 3), a finding further supported by the ROC curve (Figure 4). (Figure 3) (Figure 4) We systematically profiled clinical characteristics of all patients, such as age, gender, and other clinical factors. The ROC curve for clinical characteristics also proved that this predictive model had a better predictive ability than any independent risk factor. (Figure 5) As for DCA, Figure 6 shows its corresponding curve, where X-axis represents successful S-FTR treatment probabilities, while Y-axis represents the procedure in question’s net benefit. (Figure 6) With regard to the predictive nomogram model for S-FTR post MVR, its corresponding line (red) in the DCA curve was far away from the lines representing the probabilities for all (blue) or no patients having S-FTR (green). This indicates that the model has a high degree of practical clinical use, in that patients evaluated under it gain more health benefits than those who do not. Therefore, this predictive model would be greatly beneficial for predicting S-FTR onset, owing to its high accuracy.

DISCUSSION

FTR treatment, no matter its etiology, ultimately is based on the same rationale of interrupting the vicious cycle of FTR leading to RV volume overload, systolic dysfunction, and subsequent FTR worsening. With respect to S-FTR, in particular, its occurrence post mitral valve surgery has been reported to be 16-67%, leading to multiple researchers proposing TV-focused surgical strategies to treat FTR during MVR surgery [Izumi 2020]. However, controversy still exists regarding proper indicators and surgical protocols for mild/moderate FTR. Furthermore, these secondary TV surgical procedures, in turn, have their own issues associated with high long-term mortality [Hamadi 2019; Muntané-Carol 2021]. Therefore, in order to aid clinician decision-making as to whether TV surgery should be conducted simultaneously with MVR surgery to reduce S-FTR risk, a simple, rapid assessment method to judge a patient’s likelihood for developing S-FTR would be of great assistance. This is especially pertinent as early TV intervention could have significant implications for S-FTR risk. Our study found that 96/442 patients undergoing MVR from 2001-2015 developing S-FTR after MVR surgery, consistent with previous studies’ findings [Topolsky 2019]. As S-FTR onset in patients undergoing MVR surgery is a complex process involving multiple factors, 10 predictive indicators for S-FTR were initially included in this study, based on existing literature, expert opinions, and univariate analyses. These indicators were then subject to multivariate analysis, where age, gender, LAD, AF, PH, and TRA are found to be independent risk factors affecting long-term S-FTR likelihood in MVR patients. Their correlation with S-FTR was supported by previous studies demonstrating close associations between LAD, PH, AF, and TRA with post-mitral valve surgery FTR [Gao 2020; Mutlak 2020; Choi 2018; Bertrand 2021], owing to long-term mitral valve diseases causing left atrial expansion, atrial muscle remodeling, plus AF-causing cardiomyocyte electrophysiological and mechanical changes [Beckhoff 2018]. Sustained AF, in turn, causes atrial mechanical activity loss, resulting in various pathological processes, including hemodynamic changes, further left atrial expansion, PH from vasoconstriction and remodeling, irreversible RV myocardial damage, and gradual TA increase. These processes eventually lead to FTR, whose gradual deterioration further aggravates AF,

Table 2. Univariate and multivariate analyses for variables associated with S-FTR survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis, Odds Ratio (OR) (95% CI)</th>
<th>P-value</th>
<th>Multivariate analysis, OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.22 (0.12-0.40)</td>
<td>&lt;0.001</td>
<td>0.40 (0.21-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.10 (1.07-1.13)</td>
<td>&lt;0.001</td>
<td>1.05 (1.01-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>38.44 (19.30-76.57)</td>
<td>&lt;0.001</td>
<td>8.95 (4.14-19.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tricuspid regurgitation area</td>
<td>1.24 (1.19-1.28)</td>
<td>&lt;0.001</td>
<td>1.16 (1.09-1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No atrial fibrillation</td>
<td>0.06 (0.03-0.11)</td>
<td>&lt;0.001</td>
<td>0.26 (0.12-0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.11 (1.09-1.13)</td>
<td>&lt;0.001</td>
<td>1.06 (1.03-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricle end diastolic diameter</td>
<td>0.96 (0.94-0.98)</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Right atrial transverse diameter</td>
<td>1.11 (1.09-1.12)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Right atrial longitudinal diameter</td>
<td>1.09 (1.07-1.11)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mitral regurgitation area</td>
<td>0.98 (0.95-1.01)</td>
<td>0.04</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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PH, etc., forming a vicious cycle [Vachiéry 2019]. Therefore, this study reaffirms the connection between LAD, PH, AF, and TRA with FTR pathogenesis, which in turn is associated with left heart disease [Vachiéry 2019]. With respect to gender and age, multiple previous studies have found females are at higher risk for FTR [Choi 2018; Desai 2013], though our study specifically found this female-S-FTR correlation in the context of MVR surgery, which could be applicable to RHD cases. As for age, older patients were found in this study to have greater long-term S-FTR risk post MVR surgery, consistent with predictive factors discovered in previous publications [Mutlak 2020]. This association likely is due to older patients being previously overlooked for S-FTR diagnoses, resulting in them tending to be in the disease's late stages upon receiving surgery; this late diagnosis leads to poor prognoses. We therefore advocate, based on our findings, simultaneous MVR surgery execution with TVr being recommended more often for elderly patients to reduce FTR likelihood. It is worth mentioning, though, that MVR surgery can only reduce afterload; it is thus unable to resolve TA expansion issues, nor improve preload and right heart functioning. As a result, RV dysfunction may continue post-surgery, contributing to future FTR progression. It has been

recognized that TA diameter change is an independent FTR contributory factor. Since this study is a retrospective one, it is not considered a routine preoperative measurement parameter, though LATD and LALD can indirectly reflect TA expansion extent [Guta 2021]. In fact, our results demonstrated that no correlation between pre-surgery atrial size in multivariate analysis and long-term S-FTR likelihood is present, which is supported by other researchers, such as David et al. [David 2018]. In their case, they found an association between TA enlargement and post-surgery FTR progression being present only under <60% LV ejection fraction conditions; no correlation was present otherwise for preoperative TA values under both univariate and multivariate Cox regression analyses [David 2018]. Additionally, prospective studies conducted by Sordelli et al. [Sordelli 2016] and Bertrand et al. [Bertrand 2021] have supported TA diameter's lack of predictive value. The former group, after assessing 706 mitral valve surgery patients with 3-dimensional transesophageal echocardiography, found, respectively, reduced, unchanged, and increased FTR occurrence among 32%, 62%, and 5.5% of post-surgery patients after 2 years follow-up, while the latter group postulated that this lack of correlation between TA diameter and FTR occurrence after 2 years could be the result of pacemaker implantation interfering with FTR progression. Additionally, some risk factors, such as preoperative RV function, were not included.

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**Figure 3.** Calibration plot of the nomogram model for predicting 5-year S-FTR probability, obtained after internal validation via tenfold cross-validation by Bootstrap. Cross-spot line (solid black) represents S-FTR model prediction-actual occurrence correlation in patients, while reference (dashed grey) line indicates the occurrence of an exact match between predicted and actual S-FTR probability values. Error bars correspond to 95% confidence interval.

**Figure 4.** Receiver operating characteristic curve of the nomogram predictive model for predicting S-FTR onset within 5 years post mitral valve replacement. Area under the curve is 0.99 indicating high specificity and sensitivity for S-FTR detection.
in the predictive S-FTR nomogram model, partly owing to the paucity of literature regarding their predictive value. In particular, RV function was omitted due to the lack of a single parameter being able to adequately and consistently reflect RV dysfunction occurrence, leading to it not being routinely measured under TTE. Furthermore, RV compensatory remodeling could occur in the midst of FTR, stemming from the Frank-Starling effect being triggered among myocardial cells when FTR passes the RV afterload. This effect serves as a compensatory mechanism affecting central venous pressure, promoting that compensatory remodeling. With respect to our study, patients not undergoing TVr had low-moderate FTR, as well as normal RV function. Therefore, further confirmation is required to determine whether our nomogram model can aid in predicting FTR progression post-RV remodeling, aiding decision-making for preventative TV surgical interventions.

This study has contributed to guiding preventative FTR procedures by providing a predictive nomogram model delineating S-FTR likelihood post MVR surgery. Current clinical practice entrusts preventative TVr decision-making, particularly for mild FTR patients, on surgeons’ personal judgements, based on their experience. This could lead to TVr procedure delays and thus higher intraoperative mortality [Dreyfus 2018; Izumi 2020]. This model aids in solidifying TVr clinical decisions through its predictive capabilities, particularly in terms of discriminatory power and accuracy, for determining S-FTR risk in patients undergoing MVR, where high-risk ones would be recommended for TVr. The specific weights for the six key risk factors in the model also could aid in precision medicine, as specific interventions could be developed to mitigate their particular impact on S-FTR development. For instance, patients with increased LAD and AF could receive left atrial radiofrequency ablation and folding surgeries to treat those conditions, instead of TVr, as multiple studies have associated TVr alone with high mortality. Therefore, the model helps identify individuals most likely to benefit from TVr despite the mortality risk, versus those better off with other procedures, such as transcatheter approaches. Of course, further prospective, randomized studies are needed to determine TVr benefits among patients at risk for S-FTR, versus other intervention strategies.

Limitations: Even though we have introduced a predictive nomogram model for S-FTR after MVR, its results should be taken with caution owing to the study limitations, one of which is biases in the collected data, due to its retrospective nature. Only 442/813 patients met the study’s inclusion criteria, and among the excluded patients, 184 (22.6%) had missing data. However, 442 cases were much larger than the optimal sample size, 110-220, determined by multivariate logistic regression analysis, which was based on each independent variable requiring 10-20 samples, for a 100-200 case total, along with accounting for a 10% possible case loss. Therefore, even with omitting other patients, due in part to data collection incompleteness, 442 patients is still large enough to
guarantee data completeness and accuracy within the nomogram analysis. Additionally, even with the predictive nomogram model having demonstrated a high degree of discriminatory capability and accuracy in identifying S-FTR post-MVR surgery, more multi-central prospective studies are necessary to further support its validity, along with interventional trials to demonstrate prophylactic TVr effectiveness and safety for those high-risk patients. Another limitation is FTR severity underestimation under echocardiography, despite the technique being used in previous studies [Asmarats 2019]. Lastly, the nomogram only focused on preoperative variables and did not include intra- and postoperative factors, possibly contributing to S-FTR, such as etiology, operation length, previous valve surgery history, and resection status, etc. Further research is required to confirm the role those factors play, if any, to S-FTR, especially as prior research has overlooked them. All of these limitations will be the focus for future research, but this nomogram model still serves as a useful tool for diagnosing future S-FTR risk among post-MVR patients.

**CONCLUSION**

In this study, we have developed a novel, easy-to-use, nomogram-based model with high discriminatory capability and accuracy to predict 5-year risk likelihood for postoperative S-FTR post MVR surgery. Since TV interventions are underused and often initiated too late, the study is clearly of interest. The nomogram model may help to identify patients at risk for functional tricuspid regurgitation.

**REFERENCES**


