

Evaluation of the SAME-TT₂R₂ score to predict the quality of anticoagulation control in patients after Mitral Valve Replacement

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Research Article

Keywords: SAME-TT₂R₂ score, anticoagulation control, time in therapeutic range, mitral valve replacement

Posted Date: March 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-290512/v1>

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Abstract

Background:

This study aimed to evaluate the role of SAME-TT₂R₂ score in the prediction of anticoagulation control after mechanical mitral valve replacement.

Methods and Results:

We retrospectively reviewed clinical data of 161 patients who received mechanical mitral valve replacement at Beijing Anzhen Hospital from January 2013 to December 2013. Collected data included general information of patients, medication and smoking, postoperative embolism due to anticoagulant, bleeding complications and death information.

In the SAME-TT₂R₂ score results, the lowest score was 2 points (6.3%), the highest score was 7 points (0.7%). The number of people with 4 points was the largest, 60 people (41.4%). When the cut-off value of SAME-TT₂R₂ score was set to ≥ 4 , the sensitivity and specificity of predicting TTR $\geq 65\%$ were 69.8% and 93.1%, respectively. The Youden index was 0.629. If the cut-off value of SAME-TT₂R₂ score was set to ≤ 4 , the sensitivity and specificity of predicting TTR $\geq 65\%$ were 93.0% and 44.1%, respectively, and the Youden index was 0.371.

ROC curve evaluates the predictive power of the SAME-TT₂R₂ score for TTR $\geq 65\%$. The figure showed that when the cut-off point ≥ 4 , the best combination of sensitivity and specificity was shown (69.8% and 93.1%, respectively). The area under the curve AUC was 0.854.

Conclusions:

After mechanical mitral valve replacement, the SAME-TT₂R₂ model can effectively predict the level of TTR during the course of using oral warfarin anticoagulation, and the SAME-TT₂R₂ score ≥ 4 can be used to predict TTR $< 65\%$.

Introduction

Thrombotic complications are prone to occur after mechanical mitral valve replacement, and patients need long-term oral warfarin anticoagulation therapy. ^[1] The complications such as thromboembolism and bleeding caused by improper anticoagulation seriously affect the patient's long-term life quality and prognosis after the surgery. ^[2] TTR is an important indicator of the level of anticoagulation quality. A high score of TTR indicates that the patient's anticoagulation situation is good and the probability of anticoagulation-related complications is low. ^[3] This study found that SAME-TT₂R₂ score can effectively predict the level of TTR, which provides a reference for further improving the quality of postoperative anticoagulation.

Materials And Method

This was an observational retrospective cohort study conducted among 168 patients who underwent mechanical mitral valve replacement at Beijing Anzhen Hospital from January 2013 to December 2013. Five person lost to follow-up due to address and mobile phone number changes, and two refused the operation after review and follow-up, 161 cases were included in this study, and the loss to follow-up rate was 4.2%.

All the patients had no previous history of bleeding disorders, and they can insist on taking warfarin for anticoagulation therapy after the operation. Patients were excluded who can't adhere to the warfarin treatment after the surgery. We also excluded the patients with severe liver and kidney dysfunction, hyperthyroidism, performed coronary artery bypass grafting and aortic valve replacement during the operation and patients who were pregnant as well as patients unable to complete the follow-up.

Collected data included general information of patients, medication and smoking, postoperative embolism due to anticoagulant, bleeding complications and death information. We collected the information through telephone follow-up, outpatient review, WeChat, and in combination with the database information of the Beijing Anzhen Hospital. The INR(international normalized ratio) values of the patients during the follow-up period were recorded, In the meantime the INR cycle were monitored. The European Society of Cardiology (ESC) and the European Society of Cardiothoracic Surgery (EACTS) in 2017 released the guidelines for the management of valvular heart disease and recommended a target value of 3.0 for the INR. ^[4] But the differences between races and regions have caused large differences in anticoagulant strength from abroad. In Asia, low-dose anticoagulation is the highly recommended. ^{[5][6][7]} ^[8] Based on the previous research and practice in our heart center, we determined the target value of INR to be 1.8–2.2.

TTR calculation: TTR (time in therapeutic range, TTR) is a way to evaluate the quality of anticoagulation control. A higher TTR score can effectively reduce warfarin-related bleeding and thrombosis events. Rosendaal method was used to calculate TTR, that is to say, the time redistribution between INR of two adjacent tests was used to calculate it. ^[9] The anticoagulation quality is satisfactory when TTR score $\geq 65\%$ ^{[10][11]}.

SAMe-TT₂R₂ Score Definition: **S**: gender, 1 point for female; **A**: age, 1 point for < 60 years old; **Me**: medical history, 1 point for people with more than 2 comorbid diseases, including hypertension, diabetes, coronary artery disease Myocardial infarction, peripheral artery disease, congestive heart failure, history of stroke, lung disease, liver or kidney disease; **T**: treatment, 1 point, such as amiodarone for rhythm control; **T**: smoking (within 2 years), 2 Points; **R**: Race, 2 points for non-white. ^[12] Since all patients in our study are Chinese, the minimum score is 2 points.

Statistical Analysis

Measurement data expressed as mean \pm standard deviation($\bar{x}\pm s$), performed by normality test. Comparison of categorical data adopted the chi-square test. All tests were two-sided, and p-values were considered significant if < 0.05 . Calculations were performed using SPSS software (version 22.0). The receiver operator characteristic curve (ROC) curve was used to determine the best node and predict the performance of sub-optimal TTR. Kaplan-Meier survival curve was used to analyze the death of patients with different SAME-TT₂R₂ scores.

Results

161 patients successfully completed the follow-up research (54 males,106 females, mean age 53.4 ± 8.4 years) and the median follow-up time were 1749 (1631,2004)days. In the SAME-TT₂R₂ score results, the lowest score was 2 points (6.3%), the highest score was 7 points (0.7%). The number of people with 4 points was the largest ,60 people (41.4%). The demographic characteristics of the sample are shown in Table 1.

During the follow-up period, a total of 4087 INR examinations were performed, and the median number of INR was 2.07. The INR results between 1.8–2.2 were 2207 times, accounting for 54.0%, the INR exceeding 2.2 were 1102 times (27.0%), and the INR less than 1.8 were 778 times (19.0%). The median TTR was 43.8% (31.7%, 65.6%).

Among the various indicators for evaluating the SAME-TT₂R₂ score, apart from ethnic factors, gender factors were the most common (106, 65.8%), while the use of amiodarone for rhythm control and smoking within 2 years were the least common, both of 30 (18.6 %). (See Table 2)

When the cut-off value of SAME-TT₂R₂ score was set to ≥ 4 , the sensitivity and specificity of predicting TTR $\geq 65\%$ were 69.8% and 93.1%, respectively. The Youden index was 0.629. If the cut-off value of SAME-TT₂R₂ score was set to ≤ 4 , the sensitivity and specificity of predicting TTR $\geq 65\%$ were 93.0% and 44.1%, respectively, and the Youden index was 0.371.

ROC curve (Fig. 1) evaluates the predictive power of the SAME-TT₂R₂ score for TTR $\geq 65\%$. The figure showed that when the cut-off point ≥ 4 , the best combination of sensitivity and specificity was shown (69.8% and 93.1%, respectively).The area under the curve AUC was 0.854.

Figure 2 shows the event-free survival curve.

Table 1
– Demographic characteristics of the sample

Variable	n = 161
Female sex	106(65.8)
Age (years, media (P25, P75))	55.0 (47.5– 59.0)
hypertension	38 (26.2)
diabetes	44 (30.3)
Coronary Heart Disease	46 (31.7)
Peripheral vascular disease	2 (1.4)
Stroke	17 (11.7)
Heart failure	22 (15.2)
Lung disease	13 (9.0)
Liver and kidney disease	7 (4.8)
SAMe-TT2R2 score	
2, n (%)	9(6.3)
3, n (%)	28(19.3)
4, n (%)	60(41.4)
5, n (%)	40(27.6)
6, n (%)	7(4.8)
7, n (%)	1(0.7)
Categorical variables are shown as n (%), and continuous variables, as median (25%-75%).	

Table 2
– Prevalence of the SAME-TT₂R₂ score components

Score Component		n (%)
S	Sex (female)	106 (65.8)
A	Age (< 60 years)	76 (47.6)
Me	Medical history (> 2 comorbidities*)	70 (43.5)
T	Treatment (amiodarone)	30 (18.6)
T2	Tobacco use (within 2 years)	30 (18.6)
R2	Race (non-Caucasian)	161 (100)
*: Hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, previous stroke, congestive heart failure, lung disease, liver or kidney disease		

Discussion

In this study, we have shown for the first time that after mechanical mitral valve replacement, the SAME-TT₂R₂ model can effectively predict the level of TTR during the course of using oral warfarin anticoagulation, and the SAME-TT₂R₂ score ≥ 4 can be used to predict TTR < 65%.

Mitral valve replacement is a common surgical treatment for heart mitral valve disease. The existing artificial valves are divided into biological valves and mechanical valves. There is a high usage rate among the young population with mechanical valve due to biological valves have a certain probability of damage.^[13] At present, the most widely used anticoagulant after mechanical valve replacement is warfarin.^[14] The safety window between the effective dose of warfarin and the toxic dose is very narrow. Oral warfarin treatment requires continuous monitoring of the INR.^[15] Once there is insufficient anticoagulation strength or excessive anticoagulation strength, it will lead to bleeding and thromboembolic complications, which can be life-threatening in severe cases. The incidence of thromboembolic events after replacement ranges from 0.4–1.6% per year, and increases to 2.5% during the first postoperative month, even if the usual anticoagulation therapy is administered. Therefore, the anticoagulation quality seriously affects the quality of life of patients after mechanical valve surgery.^[16] Time in therapeutic range (TTR) is usually used as a standard to measure the quality of anticoagulation, and TTR with more than 65% or even 70% is generally considered to be ideal for anticoagulation quality, and these patients can often benefit from it.^[17]

It will be extremely beneficial for clinicians to create a simple and effective tool to predict whether the patients taking warfarin orally will achieve higher TTR. Based on this, Apostolakis et al proposed the SAME-TT₂R₂ model, which aimed to identify those patients with atrial fibrillation who need additional intervention during oral warfarin anticoagulation to achieve an acceptable level of warfarin control. When the score was 0–1, the target TTR could be reached, while the score ≥ 2 points meant TTR was poor.

Some subsequent studies have confirmed that this model can effectively predict TTR and anticoagulant adverse events. According to Chan et al. confirmed that in Chinese patients with atrial fibrillation, the SAME-TT₂R₂ score had a good correlation with TTR. When the SAME-TT₂R₂ score > 2 points, TTR had high sensitivity and negative predictive value, and the risk of ischemic stroke gradually increases with the increase of the SAME-TT₂R₂ score. ^[18] Fernando Pivatto Júnior et al. found that the SAME-TT₂R₂ score can effectively predict the TTR level of oral warfarin in patients with atrial fibrillation. For patients with a higher SAME-TT₂R₂ score (≥ 2 points), the anticoagulant effect of warfarin was poor while patients with low-risk (0–1 points) responded better to warfarin. ^[19] Rungroj et al. studied 1669 patients including 22 centers across Thailand and found that the SAME-TT₂R₂ score was the only independent predictor of sub-optimal TTR among NVAf patients treated with warfarin. ^[20] However, there are some studies that shows this score cannot do so. A systematic review and simulation meta analysis conducted by Miert et al. pointed out that although the SAME-TT₂R₂ score could predict low TTR, it's effect was limited and not very useful clinically ^[21].

Few people paid attention to the quality of anticoagulation of patients after mechanical mitral valve replacement, especially in Asia. In China, with the exception of a few large-scale cardiac treatment centers, many hospitals do not have dedicated anticoagulation clinics and anticoagulation follow-up databases. ^[22] How to quickly and effectively identify the patients with low TTR after mitral valve replacement is very important in busy clinical work. Our study observes for the first time that the proportion of TTR $\geq 65\%$ after mitral valve replacement only accounted for 29.5%, which indicates that the overall TTR of this group of patients is low, and it is similar to the situation in the entire Asian region. ^[23] ^[24] At the same time, we found that the SAME-TT₂R₂ score is significantly correlated with suboptimal INR control. SAME-TT₂R₂ score ≥ 4 points can be used to predict those patients with TTR < 65% after mitral valve replacement. The six simple clinical variables in the SAME-TT₂R₂ model can help to determine which patients may have poor anticoagulation quality after mitral valve replacement. Clinicians can more intuitively and easily identify these patients, so as to carry out more effective intervention on them. From the event-free survival curve, the overall survival rate of patients with SAME-TT₂R₂ score < 4 points is better than that of patients with SAME-TT₂R₂ score ≥ 4 points, and the sample size may be small, and there is no statistically significant difference between the two.

Our study confirms that after the mechanical mitral valve replacement, the SAME-TT₂R₂ score model can effectively predict the TTR level in the course of oral warfarin anticoagulation. The SAME-TT₂R₂ score model can help us identify those patients who may have anticoagulation complications simply and quickly, so that we can carry out early intervention, do a good job in education and strengthen monitoring, and reduce the complications caused by anticoagulation.

Limitations

This study is affected by the small sample size of a single center, and the future data will continue to be increased. The SAME-TT₂R₂ model does not include all potential factors that may affect TTR, such as drinking and genetic predisposition, which may be continuously improved in future studies.

Conclusion

After mechanical mitral valve replacement, the SAME-TT₂R₂ model can effectively predict the level of TTR during the course of using oral warfarin anticoagulation, and the SAME-TT₂R₂ score ≥ 4 can be used to predict TTR < 65%.

Abbreviations

TTR

time in therapeutic range

INR

international normalized ratio

SAMe-TT₂R₂

S, sex; A, age; Me, medical history; T,treatment; T, smoking; R, Race

Declarations

Availability of data and materials

Not applicable.

Acknowledgements

All authors participated in the design and analysis of the study and contributed to the manuscript development, data analysis, article writing, scheme design. Sincerely thank all patients who agreed to participate in this study. Database administrators of the Heart Transplant Center of Beijing Anzhen Hospital contributed to the data interpretation and no funding was received for this research.

Funding

No funding was received for this.

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Contributions

Shubin Li wrote the initial draft. All authors were involved in the concept and editing of the final version. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient.

Consent for publication

All authors have reviewed the manuscript and given consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

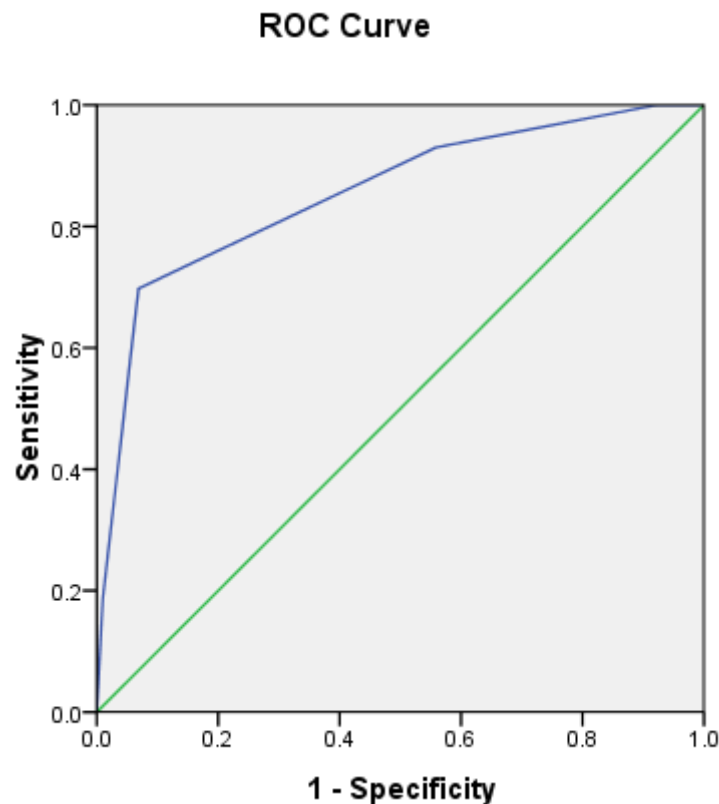


Figure 1

ROC curve for the outcome $TTR \geq 65\%$.

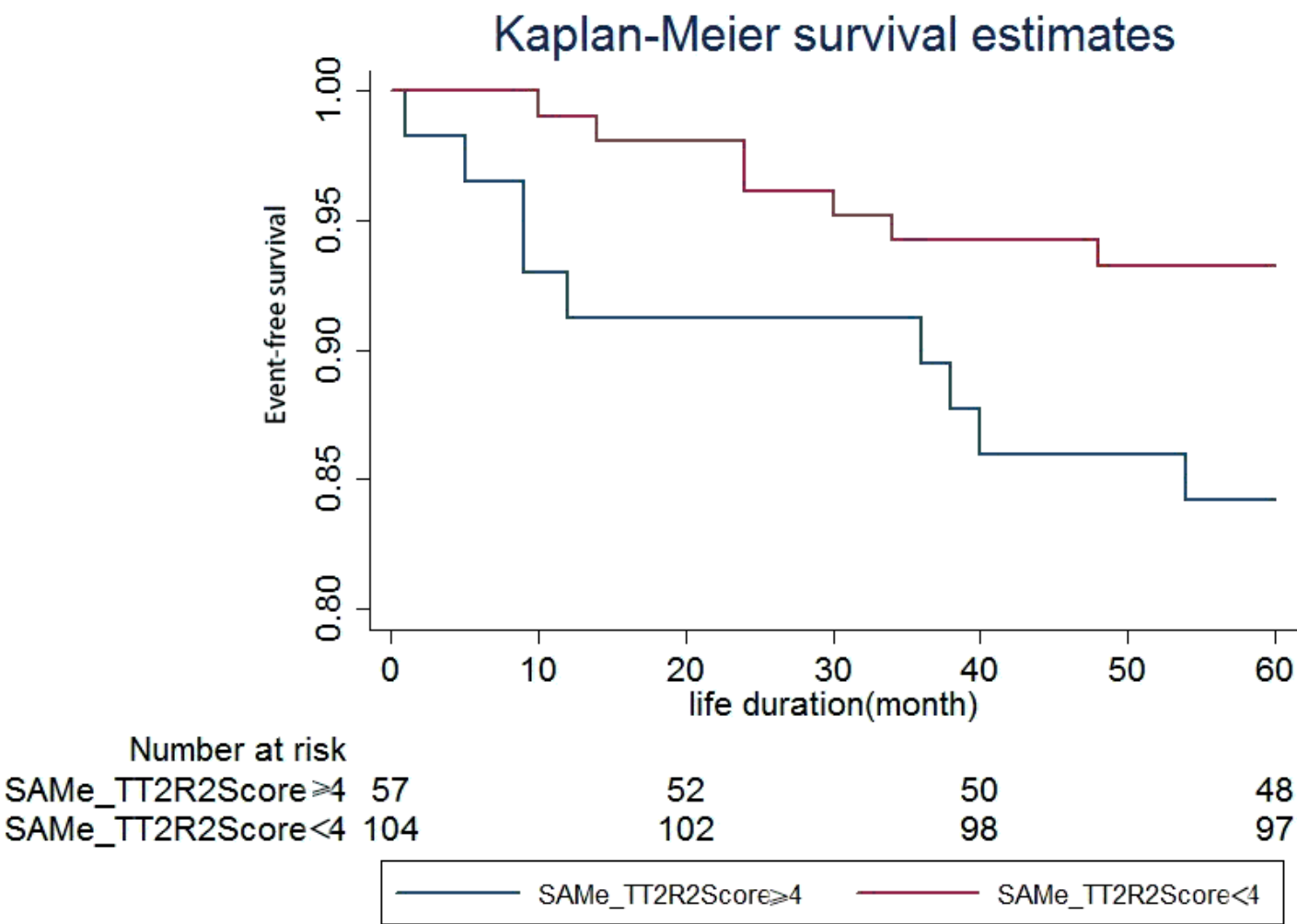


Figure 2

Event-free survival curve according to the points obtained in the SAME-TT2R2score ($p = 0.224$)