Evaluation of Longitudinal Trajectory of Functional Tricuspid Regurgitation on the Risk of Right Ventricular Dysfunction after Mitral Valve Replacement

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Abstract

Objective Functional tricuspid regurgitation(FTR) levels can vary over time and its longitudinal changing patterns may predict right ventricular dysfunction(RVD) risk. We aim to identify different trajectories of FTR in those who received mitral valve replacement(MVR) and investigate the association between longitudinal trajectory groups and RVD risk in a cohort study. **Methods and results** A prospective cohort study, reported usual FTR levels at baseline in 2005–2015 and the participants of MVR have been followed up for 5~6 years, approximately every one years, and so far, the data have been collected across five subsequent phases. Five-year longitudinal trajectories of FTR were identified using group-based trajectory modelling(GBTM). We identified 3 distinct trajectories using a GBTM, labeled by initial value and changing pattern: stable group(258/378, 68.2%), increasing-slow group(67/378, 17.6%) and increasing-fast group(53/378, 14.2%). Treating the stable group as the reference, the age- and sex-adjusted odds ratio(OR) was 25.84 (95% confidence interval, 11.78-56.65) for the increasing-slow group and 139.94(95% confidence interval, 45.47-430.68) for the increasing-fast group by logistic regression model. After adjustment for every potential confounding factors, the OR is 14.21(95% confidence interval, 4.36-46.33)、49.34(95% confidence interval, 8.88-273.87) respectively. **Conclusions** The longitudinal trajectories of worsening FTR were mostly associated with increased risk of RVD outcomes, which is independent of other factors including FTR levels. These findings have implications for intervention and prevention of RVD among individuals who received MVR.

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Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest disclosure

None declared.

Ethics approval and consent to participate

The retrospective study was approved by the Institutional Review Board with waiver of consent for retrospective data review. Privacy and personally identifiable information for all patients were protected. All baseline and clinical characteristics were obtained from the medical record of patients.

Consent for publication

Not applicable.

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ABSTRACT

Objective

Functional tricuspid regurgitation(FTR) levels can vary over time and its longitudinal changing patterns may predict right ventricular dysfunction(RVD) risk. We aim to identify different trajectories of FTR in those who received mitral valve replacement(MVR) and investigate the association between longitudinal trajectory groups and RVD risk in a cohort study.

Methods and results

A prospective cohort study, reported usual FTR levels at baseline in 2005–2015 and the participants of MVR have been followed up for 5˜6 years, approximately every one years, and so far, the data have been collected across five subsequent phases. Five-year longitudinal trajectories of FTR were identified using group-based trajectory modelling(GBTM). We identified 3 distinct trajectories using a GBTM, labeled by initial value and changing pattern: stable group(258/378, 68.2%), increasing-slow group(67/378, 17.6%) and increasing-fast group(53/378, 14.2%). Treating the stable group as the reference, the age- and sex-adjusted odds ratio(OR) was 25.84 (95% confidence interval, 11.78-56.65) for the increasing-slow group and 139.94(95% confidence interval, 45.47-430.68) for the increasing-fast group by logistic regression model. After adjustment for every potential confounding factors, the OR is 14.21(95% confidence interval, 4.36-46.33)、49.34(95% confidence interval, 8.88-273.87) respectively.

Conclusions

The longitudinal trajectories of worsening FTR were mostly associated with increased risk of RVD outcomes, which is independent of other factors including FTR levels. These findings have implications for intervention and prevention of RVD among individuals who received MVR.

Key words

Functional tricuspid regurgitation, Longitudinal trajectory, Right ventricular dysfunction, Mitral valve replacement, Cohort study

Introduction

Functional tricuspid regurgitation(FTR) is the result of geometric changes in valve structure in the absence of valve structural lesions[1]. By far, FTR is most commonly associated with pulmonary hypertension(PH) or left heart disease, primarily due to right ventricular remodeling, resulting in lobular tethering and tricuspid valve annulus(TA) dilation[2, 3]. There is increasing evidence that FTR is not only a marker of concurrent cardiac disease, but also a potential driver of adverse cardiovascular events[3]. With the in-depth study on long-term follow-up management and prognosis of patients undergoing mitral valve replacement(MVR), the old idea that FTR can be improved after MVR has disappeared, and postoperative FTR can further aggravate or cause right ventricular dysfunction(RVD)[4]. Therefore, close follow-up of patients undergoing MVR is proposed to seek surgical intervention in FTR before severe RVD occurs[5, 6]. However, this follow-up process usually takes years to decades, giving clinicians ample time to intervene with FTR to prevent or delay disease progression and thereby improve patients' long-term prognosis. Given the current challenges in the management of FTR after MVR, it is important to correctly understand the association between FTR and RVD. Always, several studies have verified a single FTR or cumulative FTR levels associated with postoperative RVD, but doesn't take into account the FTR this progressive disease throughout the postoperative changes of the potential impact and over time, FTR level and FTR trajectory may occur large individual differences, FTR of long-term dynamic model can more accurately reflect the link[3]. As normal FTR levels may go unnoticed in clinical practice and there are few studies on the relationship between FTR longitudinal trajectory and RVD after MVR at home and abroad. Consequently, in this research, the Group Based Trajectory Modeling (GBTM) model was used to identify and evaluate the trend characteristics of FTR change trajectory after MVR, so as to explore its impact on late RV function.

Materials and Methods

Ethics approval and consent to participate

The retrospective study was approved by the Institutional Review Board with waiver of consent for retrospective data review. Privacy and personally identifiable information for all patients were protected. All baseline and clinical characteristics were obtained from the medical record of patients.

Study Population and Cohort Design

Using convenient sampling method, we retrospectively analyzed clinical, hemodynamic, and echocardiographic data of consecutive 893 patients who underwent MVR between 2005 and 2015 at the Second Affiliated Hospital of Harbin Medical University were involved between2005 and 2015. The patients' cardiologists and cardiac surgeons individually made the decision to undergo either surgical intervention or medical management. For study inclusion, patients who underwent MVR 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, 3) had symptoms of right heart failure(RHF), and 4) incomplete follow-up data. Of course, they did have at least one measures of FTR every year during the five years of follow-up. FTR were measured at any of these time points if they subsequent visited at any point between the current time point and the prior pre-specified time point. At the same time, the sample size was estimated, and weighing the requirement that the group development model sample size should be 300-500 cases to ensure the model stability according to the logical proportional risk regression model. Based on these criteria, the study ultimately examined 378 patients (Figure. 1). The average number of examinations was 8.7, and the average time interval between examinations was one year during the whole follow-up period.

Data Collection and Follow-up

A complete transthoracic echocardiographic study, including complete M-mode, 2-dimensional, and Doppler analyses was performed just before the MVR were adopted and after a mean follow-up of one year, following the American Society of Echocardiography and European Society of Cardiovascular Imaging guidelines recommendation. Additional echocardiography examinations were performed when deemed necessary by the physician. At the outpatient clinic, routine echocardiography was performed approximately every six months. Parameters measured for each patient by transthoracic echocardiography(TTE) obtained from the echocardiography reports within the ultrasound database, including left atrial diameter(LAD)、tricuspid regurgitation area(TRA)、mitral regurgitation areas (MRA)、 transverse diameter of right atrium(RATD)、longitudinal diameter of right atrium(RALD)、left ventricular end diastolic diameter(LVEDD)、left ventricular end systolic diameter(LVESD)、right ventricular diameter(RVD)、Atrial fibrillation (AF) and PH. PASP was derived from the peak FTR velocity using the simplified Bernoulli equation, adding the right atrial pressure estimated from inferior vena cava diameter and collapsibility[8]. All measurements were obtained from the last ultrasound report before surgery and were evaluated in accordance with internationally recommended standards TTEs[9]. Echocardiographic exams were performed by expert trained physicians in each center, and data were revised in blind by two independent expert physicians of the core center according to previously published methods.

Outcome and Definition of Right Ventricular Dysfunction

The outcome was RVD, which was defined as the presence of severe right ventricular dilation and interventricular septal flattening (determined qualitatively by the clinician performing TTE). Tricuspid annular plane systolic excursion(TAPSE) is easily obtainable and is a measure of RV longitudinal function. TAPSE<16 mm indicates RV systolic dysfunction[9]. Anatomical M-mode was applied on the focused apical 4-chamber view of the RV to measure TAPSE. Heart failure that required inotropes for left heart failure with elevated pulmonary capillary wedge pressure(PCWP) or pulmonary congestion caused by inadequate LVAD pump speed or aortic valve insufficiency was not considered RVD. Preoperative moderate FTR was not surgically treated when the MVR was implanted and was controlled preoperatively with specific medication for HF, volume optimization and medication to decrease pulmonary vascular resistance if PH was present.

Statistical Analysis

Data are shown as mean±standard deviation for continuous variables or as number (%) for categorical variables. To identify distinct baseline to 5-year FTR risk trajectories, we used group-based trajectory models in a Stata plugin program (Stata Proc Traj). It identifes individuals' clusters following a similar underlying trajectory on the dependent variable over time within a population, based on a maximum likelihood method. We developed different models by varying numbers of groups, ranging from two to five groups, and shapes (linear, quadratic, and cubic). We then compared them using Bayesian Information Criteria (BIC) and a sufficient proportion of participants in each subgroup. To ensure the adequacy of the selected model, we assessed four models that fit diagnostic criteria as suggested by Nagin: (1) average posterior probability of assignment for each group (AvePP) equal to 0.7 or greater for all groups; (2) the odds of correct classification (OCC) equal to 5 or higher for all groups; (3) similarity between the proportion of a sample assigned to a specific group and the group probabilities estimated from the model; and (4) narrow CIs of the estimated proportion. After identifying FTR longitudinal trajectory groups, we evaluated the associations of trajectory subgroup membership (as a categorical exposure) with incident RVD after the five examination cycle using logistic regression model. Statistical significance was considered using a two-sided P <0.05. All analyses were performed using SPSS 26.0 statistical software and STATA 14.2 statistical software.

Results

Characterization of Trajectories of FTR

According to GBTM model grouping selection, three different FTR longitudinal trajectory groups were determined in patients undergoing MVR(Figure 2), with polynomial order 1, 2 and 2 respective-

ly(Supplementary table 1), including "stable group"(258 cases, 68.2%), "increasing-slow group"(67 cases, 17.6%), and "increasing-fast group"(53 cases, 14.2%). In terms of model validation, the AvePP were all greater than 0.7(Supplementary table 2), the number of people assigned to each track group was close to the estimated value of the model(Supplementary table 3), and the occurrence ratios of correctly assigned to the track group were all greater than 5(Supplementary table 4), indicating that the model fitting was ideal. Table 1 shows preoperative clinical characteristics for all patients. The length of medical history, age, female, complications of AF and PH, LAD, TRA, RATD, RALD and LVEDD showed significant difference among the three different FTR longitudinal trajectory groups(p ¡0.05).

Logistic Regression Analysis of the Impact of RVD at 5 Years Postoperatively Factors

A generalization of the GBTM model was used to link different baseline(before MVR) measures with FTR trajectory group membership while control every potential confounding factors at baseline. Three different generalizations of the GBTM model were fitted(table 2). Treating the stable group as the reference, the increasing-slow group and the increasing-fast group were all risk factors for RVD. odds ratio(OR) value and 95% confidence interval(CI) were 33.77(95% CI, 15.97 -71.39), 180.92(95% CI, 61.64 -531.06); Treating the stable group as the reference, the age- and sex-adjusted OR was 25.84(95% CI, 11.78-56.65) for the increasing-slow group and 139.94(95% CI, 45.47-430.68) for the increasing-fast group by logistic regression model. After adjustment for every potential confounding factors(age, sex, length of medical history, AF, PH, LAD, RATD, RALD, LVEDD, TRA), compared with the stable group, the OR was 14.21(95% CI, 4.36-46.33) for the increasing-slow group and 49.34(95% CI, 8.88-273.87) for the increasing-fast group by logistic regression model.

Discussion

Longitudinal Trajectory Characteristics of FTR

Left heart valve surgery can only reduce the afterload, but cannot solve TA dilation or improve the preload and RV function, and there is still a possibility of FTR progression in the long term[6]. In this study, GBTM model, a statistical method, was adopted to consider FTR information and FTR changes of multiple measurements, and finally realized the transformation from "FTR at a single time point or cumulative FTR level exposure" to "dynamic FTR longitudinal trajectory". According to grouping selection basis of GBTM model, the study determined three postoperative FTR longitudinal trajectory groups, namely "stable group", "increasing-slow group" and "increasing-fast group". Among them, patients belonging to the "stable group" always had a low postoperative FTR level, and no significant change was observed within 5 years after surgery. Patients in the " increasing-slow group" had a continuous worsening of FTR after MVR, and the severity of FTR was still less than 10.0 cm2 at the end of follow-up. Patients assigned to the " increasing-fast group" had relatively large baseline FTR, which continued to rise rapidly after MVR and deteriorated to severe FTR about 3 years after surgery. Although there has been no literature discussion on the longitudinal trajectory of FTR in the past, this study is consistent with the results of relevant studies in recent years, and FTR of some patients will deteriorate to varying degrees with the extension of postoperative time[10].

Comparison of FTR Trajectories between Groups

According to relevant literature, FTR further deteriorates after left heart valve surgery, which will reduce long-term survival and cardiac function and reduce the quality of life of surviving patients even without right heart insufficiency and severe PH[11]. Postoperative FTR deterioration is the result of multiple factors and the mechanism is complex. Currently, the mechanism recognized by many scholars is: long-term left heart valve lesions lead to left atrium enlargement, atrial muscle remodeling, and changes in electrophysiological environment and mechanical activity of cardiac cells, leading to AF eventually[12]. Persistent AF can make atrial mechanical loss cause hemodynamic changes, in the left atrium formed eddy current to make it further expanded, pulmonary vasoconstriction and refactoring to PH, right ventricular myocardial irreversible damage occurs, three pointed leaf TA gradually expand, in turn, lead to FTR, FTR deteriorating and will further aggravate the AF, PH, etc., a vicious circle has been formed[13]. A retrospective analysis of the preoperative data of the three longitudinal trajectory groups showed that with the increasing speed of FTR trajectory,

the length of medical history, LAD, complications of AF and PH, TRA, RATD, RALD, and LVEDD also gradually increased, which could explain the mechanism of worsening FTR. It was also further confirmed that there is an inseparable link between the progression of FTR and left heart valve disease[14].

The Longitudinal Trajectory of FTR is Associated with RVD

At present, studies on the relationship between the severity of FTR and the incidence of RVD are still controversial[15]. In this study, different longitudinal trajectory of FTR changes in patients after MVR was combined with RVD outcome events, reflecting the internal relationship between the two to some extent. This study found that the severity of preoperative FTR increased the risk of postoperative RVD, which was consistent with the results of previous studies[14]. The severity of traditional single FTR measurement could not explain whether the risk of future RVD would change with the change of FTR. In this study, GBLM fitting was used to find that the cumulative incidence of RVD was different in the groups with different FTR trajectory 5-year after MVR, and the cumulative incidence of RVD was the highest in the increasing group. Furthermore, logistic regression model and adjustment for multiple potential confounding factors confirmed that the upward trend of FTR longitudinal trajectory was an independent risk factor for RVD after MVR. Continuous FTR deterioration leads to irreversible remodeling of RV, further dilation of TA, increased diastolic pressure of the RV, ventricular septum shift to the left ventricle(LV), limitation of filling of the LV due to it was compressed, of the LV further increase of diastolic pressure and PASP, and ultimately RVD[15]. FTR may influence central venous pressure through RV after load and trigger the Frank-Starling compensation mechanism of RV cardiomyocytes, thereby promoting RV compensatory remodeling. However, although the degree of FTR in some patients is relatively mild, the pulmonary vascular structure and RV myocardial tissue have undergone irreversible changes[16]. The decision to perform isolated tricuspid valve surgery remains challenging due to the limited data available to guide preoperative evaluation and the lack of preoperative optimization strategies. Patients undergoing MVR were denied second surgical intervention for tricuspid valve due to contraindications such as ventricular dysfunction and pulmonary vascular disease caused by worsening FTR, resulting in delayed FTR treatment and high intraoperative mortality[17-19]. Therefore, preoperative FTR severity cannot be used as the only indication for simultaneous tricuspid valve surgery. The results of this study further suggest that clinicians should pay attention not only to the severity of a single FTR, but also to the longitudinal trajectory of postoperative FTR. At the same time, questions are also raised about existing guidelines and clinical practice: The worsening of FTR after MVR increases the risk of RVD. Should intervention be taken for these patients in clinical work? How to detect patients with rapidly increasing FTR trajectory and what intervention measures should be taken? In the future, further prospective big data studies, postoperative follow-up and exploration of etiology will contribute to accurate discussion. Based on high-quality observational scientific paper, the guidelines note that tricuspid valve repair(TVr) during MVR does not increase surgical risk and may reverse RV remodeling[20, 21]. Taken together, we believe that no matter whether patients have normal TV function and anatomical structure before MVR, clinicians should pay attention to the existence of FTR, especially for patients with an increasing trend of FTR change. In order to avoid RVD in these patients, it is better to perform MVR while preventing tricuspid valve surgery.

Limitations of this study: 1.The retrospective observational design and were from the same research center, which was slightly less representative, and it was a northern population of China with strong regional characteristics. In the future, large sample and multi-center studies can be carried out to explore the evolutionary characteristics of FTR in MVR patients and the influencing mechanism of RVD; 2.In the evaluation of the relationship between FTR longitudinal trajectory group and RVD, although possible confounding factors were corrected as far as possible, other confounding factors, such as right heart function, were not corrected. At the same time, values cannot be compared across different ultrasound platforms; 3.Follow-up of 5 years, this study was to build FTR longitudinal trajectory group only based on the five times when the follow-up results, may not be able to fully reflect the change of each individual, and thus underestimated FTR longitudinal trajectory levels influence on RVD; 4.The comprehensive assessment of RV function requires the combination of multiple parameters. The definition of RVD only depended on TAPSE in our study.

This paper has used a novel statistical approach to report complex longitudinal data, and supports the notion that the long-term trajectories of worsening FTR in patients with regular follow-up after MVR were generally associated with increased risk of RVD outcomes. It is of great clinical significance for clinicians to identify high-risk patients as soon as possible and execute personalized intervention, avoid RHF, decrease patient re-hospitalization rate and allocate medical resources rationally. Future studies should address the underlying mechanisms and examine whether findings of our study can be translated into prevention and intervention measures.

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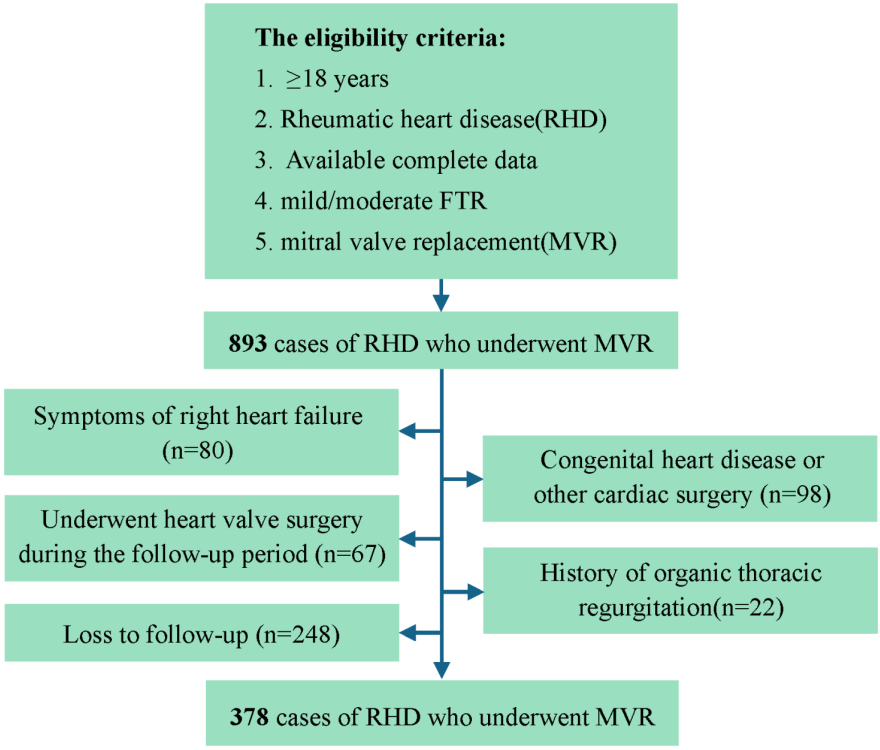

Figure 1. Flowchart for patient of rheumatic heart disease(RHD) inclusion in the retrospective analysis. After applying exclusion criteria (congenital heart disease, follow-up loss, organic thoracic regurgitation [TR] history, heart valve surgery during follow-up period), 378 patients were included.

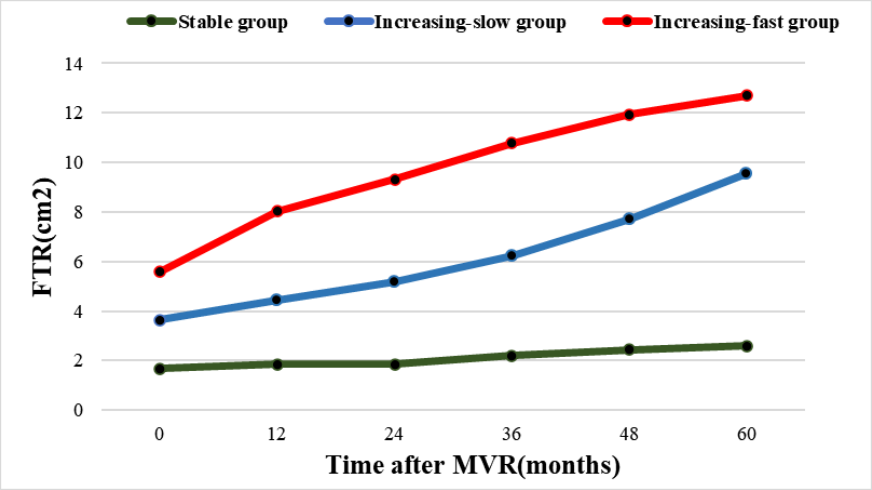

Figure 2. Different FTR longitudinal trajectory groups of the study population after MVR.

Table 1. Clinical characteristics of the study population

Preoperative variables	**Stable group (n=258)**	**Increasing-slow group(n=67)**	**Increa**
Duration of medical history (months)	69.00±82.77	143.32±115.34	147.98
Age (years)	48.74±9.18	54.78±7.29	56.30±
Female, n (%)	58.53	77.61	83.02
Body mass index (kg/m^2)	24.35±7.72	22.74±3.47	23.39±
Systolic blood pressure (mmHg)	123.13±18.09	124.25±19.68	122.57
Diastolic blood pressure (mmHg)	82.36±11.85	83.64±9.127	85.53±
Heart rate (bpm)	77.34±12.04	76.94±13.28	74.92±
Left ventricular ejection fraction (%)	60.29±6.25	60.72±5.39	60.35±
Atrial fibrillation, n (%)	29.07	76.12	88.68
Mild pulmonary arterial hypertension, n (%)	10.47	68.66	88.68
Left atrial diameter (mm)	43.59±6.14	53.10±9.18	55.97±
Tricuspid regurgitation area(cm^2)	2.04±1.45	4.84±2.67	6.60±3
Mitral regurgitation area(cm^2)	7.43±6.83	6.97±7.87	7.26±6
Right atrial transverse diameter (mm)	39.99±5.92	48.41±8.14	51.46±
Right atrial longitudinal diameter (mm)	47.25±6.34	55.54±7.49	59.70±
Left ventricular end diastolic diameter (mm)	48.26±7.47	50.38±9.20	51.57±
Left ventricular end systolic diameter (mm)	32.73±7.79	31.57±7.09	33.65±
Right ventricular dilation (mm)	18.85±3.30	18.63±3.80	17.61±
Pulmonary artery diameter (mm)	25.18±4.99	25.458±5.66	24.52±
Aspartate transaminase/alanine transaminase ratio	1.21±0.65	1.37±0.91	1.46±0
Creatinine (umol/L)	89.21±53.17	89.56±56.16	91.59±
Blood urea nitrogen (mmol/L)	7.69±3.65	6.891±2.74	8.61±1
NYHA classification, n (%)			
II	37	12	8
III	197	46	41
IV	24	9	4

Table 2. Sensitivity of different FTR longitudinal trajectory groups on RVD [OR(95%CI)].

Model	**Groups**	**B**	**SE**	**Wald**	***P*-valve**	**OR(95% CI)**
Model 1	Stable group	-				
	Increasing-slow group	3.519	0.382	84.882	¡0.001	33.77(15.97-71.39)
	Increasing-fast group	5.198	0.549	89.518	¡0.001	180.92(61.64-531.06)
Model 2	Stable group	-				
	Increasing-slow group	3.252	0.401	65.883	¡0.001	25.84(11.78-56.65)
	Increasing-fast group	4.941	0.574	74.222	¡0.001	139.94(45.47-430.68)
Model 3	Stable group	-				
	Increasing-slow group	2.577	0.469	30.258	¡0.001	13.16(5.25-3.97)
	Increasing-fast group	4.047	0.634	40.778	¡0.001	57.20(16.52-198.57)
Model 4	Stable group	-				
	Increasing-slow group	2.654	0603	19.366	¡0.001	14.21(4.36-46.33)
	Increasing-fast group	3.898	0.875	9.870	¡0.001	49.34(8.88-273.87)

Note:

Model 1 : Right heart failure was taken as the dependent variable, and different FTR trajectories were taken as independent variables (the stable group was taken as the control group);

Model 2: Based on Model 1, age and gender were corrected;

Model 3: Based on Model 2, the length of history, atrial fibrillation and pulmonary hypertension were corrected.;

Model 4: On the basis of Model 3, left anteroposterior atrial diameter, right atrial transverse and longitudinal meridian, left ventricular end diastolic diameter, right ventricular diameter and tricuspid valve regurgitation area were corrected.