

## Research Article

# Right Ventricular Involvement in Takotsubo Syndrome

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## Abstract

**Objective:** Patients with Right Ventricular (RV) involvement Takotsubo Syndrome (TTS), which leads to the higher risk of potential clinical comorbidities, higher mortality and extended recovery should be treated appropriately in the early stage, however, currently large-scale clinical data are lacking. Our article reviews epidemiological, clinical and prognostic features of RV TTS in our hospital.

**Methods:** This group study retrospectively evaluated patients diagnosed as TTS. Ventricular involvement was defined on wall motion abnormality showed by left ventriculography and echocardiography. The recovery of ejection fraction and pulmonary hypertension, defined as prognosis were assessed at followed-up.

**Results:** Among 15 patients, diagnosed as TTS, 8(57.1%) were assigned to the Biventricular involvement TTS (Bi-VTTS). Older ((70.33±8.37 vs 69.00±10.51), P=0.04), women (8(88.9%), P=0.041) with lower LVEF (<50%) (8 (88.9%), P=0.020) were risky for RV TTS. At admission, for patients with RV TTS, LVEF was lower, B-type natriuretic peptide levels increased significantly ((591.9±162 vs 362.4±116.4pg/ml), P=0.021), elevations of troponin T and CK-MB were not statistically significant, changes of Electrocardiograms (3(33.3%), P=0.020), myocardial edema and myocardial fibrosis also showed by Late Gadolinium Enhancement (LGE) of Cardiac Magnetic Resonance (CMR). During the index admission, hydrothorax (9(100%), P=0.001), shock (1(20%), P=0.164), chronic heart failure (2(40%), P=0.158), thrombus (9(100%), P=0.001), aneurysm (1(11.1%), P=0.143), mitral and tricuspid regurgitation (moderate or higher) (7(77.8%), P=0.180) and aortic regurgitation (moderate or higher) (3(33.3%), P=0.103) were associated with RV TTS. Except one patient (22.2%) died, longer time recovery and poor prognosis were assessed by ejection fraction and pulmonary hypertension.

**Conclusions:** Patients with the RVTTS, normally given the higher risk of potential clinical comorbidities, higher mortality and extended recovery who should be treated appropriately in the early stage to reduce comorbidities events, and improve patient prognosis.

## Introduction

Takotsubo Syndrome (TTS) is an acute heart failure syndrome characterized by Left Ventricular (LV) dysfunction and peculiar patterns of Wall Motion Abnormalities (WMA) [1]. Although this condition typically affects left ventricular triggered by emotional or physical event, since 2000 [2,3]. reported the first case of simultaneous left and right ventricle involvement, that is, a case of biventricular TTS (Bi-V TTS), which aroused the attention of the medical community and the number of cases and clinical studies of right ventricular involved TTS(RV TTS) gradually increased [4,5]. Reported the first case of TTS that occurred only in the right ventricle, afterwards, isolated right ventricle Takotsubo cardiomyopathy and isolated right ventricular balloon-like syndrome were gradually recognized. Although the final outcome of right ventricular involvement is not bad, it still has a strong correlation with poor prognosis of TTS, more severe left ventricular dysfunction, high incidence of hemodynamic instability, and long-term increased mortality [6-8]. The current research and clinical data on RV TTS are insufficient, only limited case reports and case studies, so the epidemiology, clinical characteristics and pathogenesis of right ventricular involvement with or without

left ventricular involvement TTS remain unclear [9]. Clinicians need to understand the clinical characteristics and imaging manifestations of TTS with right ventricular involvement to detect right ventricular involvement, avoid missed diagnosis, treat patients appropriately in order to reduce adverse events and mortality.

## Methods

### Study Population

Data were collected from the Department of cardiology, Affiliated Drum Tower Hospital, Medical School of Nanjing University from 2012 to 2018. TTS was defined based on modified Mayo Clinic Diagnostic Criteria and all cases of TTS diagnosis made according to Mayo Clinic Diagnostic Criteria were posteriori compared with the new Inter TAK Diagnostic Criteria. Ventricular involvement was defined based on wall motion abnormality showed by left ventriculography and echocardiography. Within 90 minutes from hospital admission, coronary angiography must be performed for patients presenting persistent ST-segment elevation, within 48 hours for patients presenting non-ST-segment elevation and within 120 minutes for patients presenting haemodynamic instability.

Echocardiography was performed immediately at hospital admission. Medical records were reviewed by investigators at the Department of cardiology, Affiliated Drum Tower Hospital, Medical School of Nanjing University. Uncertain cases were reviewed by core team members, for inclusion or exclusion of cases, the decisions were reached by consensus. Follow-up information came from medical records, telephone interviews, or clinical visits.

### PPI Statement

Our study protocol was reviewed by respective local ethics committee and investigational review board at Department of cardiology, Affiliated Drum Tower Hospital, Medical School of Nanjing University. Considering the partly retrospective nature of our study, the needs for informed consent of most studies were waived by ethics committees.

### Analysis

Patients were divided into 2 groups based on the presence or absence of right ventricular involvement. Echocardiography, Cardiac magnetic resonance imaging, and Blood test of cardiac biomarkers were used for comorbidities assessment [10,11]. Recovery analysis was followed up by Echocardiography and accordingly, patients' admission, discharge and return visit time, we analyze the recovery of ejection fraction and pulmonary hypertension, which were compared to initial data when patients in the hospital. Patients who haven't undergo through Percutaneous coronary intervention but diagnosed as TTS were still credited to data analysis.

### Statistical Analyses

Continuous variables were presented as mean±SD or median with interquartile range, whereas categorical variables were reported as frequency with percentage. Continuous variables were compared using the Mann-Whitney U test, whereas the Pearson  $\chi^2$  test (or Fisher exact test, as appropriate) was used for the comparison of categorical variables. Recovery estimates were assessed using Kaplan-

Meier curves, and group differences were evaluated with the log-rank test. The cut-off for statistical significance was set at a 2-sided P value <0.05. Odds ratios were reported with the respective 95% CIs. Analyses were computed with statistical software (SPSS V23.0, IBM Corp). Figures were created with Prism 7 software (GraphPad).

## Results

Of 15 patients, diagnosed as TTS, 14 patients underwent coronary angiography and left ventriculography, among those 14 patients, combined with their echocardiography, 8(57.1%) were assigned to the Bi-V TTS, 5(35.7%) were assigned to the LV TTS and only 1(7.14%) were assigned to the RV TTS referred to (Table 1). We divided those patients into two groups, Bi-V or RV TTS group and LV group.

For the incentives and first symptoms: our cases indicated that the triggers of RV TTS and LV TTS were basically similar, usually caused by acute emotional or physical disease stress, such as death of relatives and friends, sudden physical illness, brain disease, pheochromocytoma etc., however, among those cases it was obvious that older ((70.33±8.37 vs 69.00±10.51), P=0.04), women (8 (88.9%), P=0.041) with lower left ventricular ejection fraction (LVEF<50%) (8(88.9%), P=0.020) had a high risk for RV TTS. On the day of admission, for general condition of the patients, LVEF of RVTTS was lower than TTS without right ventricular involvement, B-type natriuretic peptide levels increased significantly with RV TTS (591.9±162 vs 362.4±116.4pg/ml), P=0.021), the elevation of troponin T and CK-MB values with right ventricular involvement compared with TTS without right ventricular involvement was not statistically significant. Those myocardial injury markers were mostly elevated during the acute episode, which was similar to Acute Coronary Syndrome (ACS), and was easily misdiagnosed as ACS, but the increase was not directly proportional to the degree of abnormal wall motion, then decreased rapidly in recovery [12]. Electrocardiograms of right ventricular affected TTS mostly had changed of ST-segment elevation, ST segment flat (2(22.2%), P=0.036), T wave inversion,

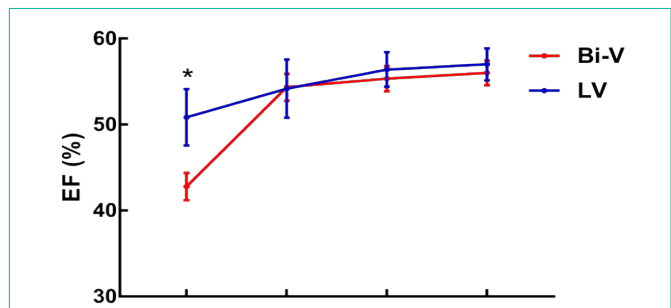
**Table 1:** Involvement diagnosis.

	LV wall motion abnormality	RV wall motion abnormality	Compensatory contraction enhancement	ST segment elevation	Coronary artery obstructed	diagnosis
Patient 1	Apical	Apical	LV Basal	Anteroseptal	LCX Mid-distal stenosis 85%	Bi-V TTS
Patient 2	Apical	None	None	Lateral, Posterior	None	LV TTS
Patient 3	Apical	Apical	Anterior, Inferior	Inferior	RCA PDA 30%	Bi-V TTS
Patient 4	LV Anterior, Apical	Apical	Basal	Anterior-Inferior	LAD Mid stenosis 30%	Bi-V TTS
Patient 5	LV Apical	None	Basal	Anterior	LAD Mid stenosis 30%	LV TTS
Patient 6	Apical, LV Anterior, Inferior	Anterolateral, Inferior	Basal	None	LAD Proximal stenosis 30%	LV TTS
Patient 7	Mid LV Anterior	RV Apical	Small Portions	Anteroseptal	None	RV TTS
Patient 8	Apical	None	Basal	Anterior	None	LV TTS
Patient 9	LV Apical	None	Basal	None	None	LV TTS
Patient10	Apical	Apical	Basal	Anteroseptal	LAD D1 30% RCA PDA 20%	Bi-V TTS
Patient11	LV Anterior, Apical	Apical	Basal	Inferior, Anterior	LCX OM 50%	Bi-V TTS
Patient12	LV Apical	RV Basal	Basal	Anteroseptal	RCA PL 30%	Bi-V TTS
Patient13	Apical	Apical	Basal	Extensive Anterior	None	Bi-V TTS
Patient14	Anterior, Apical	Apical	LV Basal	Anteroseptal, High lateral	LAD Proximal stenosis 30%	Bi-V TTS

TTS: Takotsubo Syndrome; LV: Left Ventricle; RV: Right Ventricle; Bi-V: Biventricular; LAD: Left Anterior Descending Artery; LCX: Left Circumflex Artery; RCA: Right Coronary Artery; D: Diagonal Branch; PDA: Posterior Descending Artery; OM: Obtuse Marginal Branch; PL: Posteriolateral Branch

**Table 2:** Patient admission.

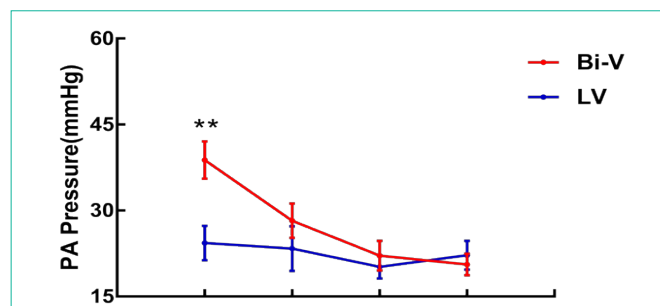
	Bi-V or RV (n=9)	LV (n=5)	P
Sex (women, %)	8(88.9%)	4(80%)	0.041
Age, y	70.33±8.37	69.00±10.51	0.043
Preceding events	5 (55.6%)	3 (60%)	0.420
BNP (pg/ml)	591.9 ± 162	362.4 ± 116.4	0.021
cTNT (ug/l)	0.419 ± 0.081	0.804 ± 0.330	0.168
EF decline (<50%)	8 (88.9%)	3 (60%)	0.020
<b>ECG characteristics</b>			
ST segment elevation	8 (88.9%)	4 (80%)	0.649
ST segment flat	2 (22.2%)	4 (80%)	0.036
T-wave inversion	8 (88.9%)	4 (80%)	0.649
Q waves	1 (11.1%)	2 (40%)	0.020
Coronary artery obstruction (%)	2 (22.2%)	0 (0%)	0.158
<b>Comorbidities</b>			
Hydrothorax	9 (100%)	1 (20%)	0.001
Heart failure	7 (77.8%)	2 (40%)	0.158
Thrombus	1 (11.1%)	0	0.143
Shock	1 (20%)	0	0.164
Aneurysm	1 (11.1%)	0	0.164
Mitral and tricuspid regurgitation (moderate or higher)	7 (77.8%)	3 (60%)	0.180
Aortic regurgitation (moderate or higher)	3 (33.3%)	2 (40%)	0.103



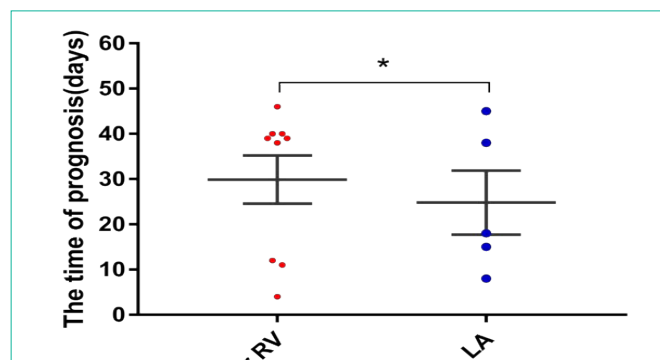
**Figure 1:** LVEF was lower for those patients with right ventricular involvement at admission day, although after appropriate treatment, their LVEF back to almost normal when discharge from the hospital, usually 10 days at the average, for the long-term prognosis, the deterioration of LVEF would appear in the patients of right ventricular involvement TTS. Bi-V: Biventricular; LV: Left Ventricle.

QRS low voltage, and pathological Q waves (1(11.1%), P=0.020), etc. referred to (Table 2), which often involving the entire chest lead (V1 ~ V6) and the inferior ( , , aVF). In the Cardiac Magnetic Resonance (CMR) imaging, T2-weighted sequence of CMR could show myocardial edema, although the left and right ventricular ejection fractions had basically returned to normal, myocardial edema persists and it was continued to 1 month later. With Late Gadolinium Enhancement (LGE) of CMR can indicate the presence of myocardial fibrosis in some cases [13], however, compared with acute myocardial infarction, the TTS signal intensity was lower and the range was smaller.

For comorbidities while in hospital nine patients with RVTTS



**Figure 2:** Pulmonary Hypertension was higher for those patients with right ventricular involvement at admission day, although after appropriate treatment, their Pulmonary Hypertension back to almost normal when discharge from the hospital, usually 10 days at the average, for the long-term prognosis, the recovery of Pulmonary Hypertension would longer time for the patients of right ventricular involvement TTS. Bi-V: Biventricular; LV: Left Ventricle.



**Figure 3:** Longer time of recovery needed and poor prognosis achieved for patients with right ventricular involvement TTS. Bi-V: Biventricular; LV: Left Ventricle.

happened to have hydrothorax (9(100%), P=0.001), others such as severe shock (1(20%), P=0.164), chronic heart failure (2(40%), P=0.158), thrombus (9(100%), P=0.001), aneurysm (1(11.1%), P=0.143), mitral and tricuspid regurgitation (moderate or higher) (7(77.8%), P=0.180) and aortic regurgitation (moderate or higher) (3(33.3%), P=0.103) happened in certain risk as well, but not very significant referred to (Table 2). Because RV TTS affected both left and right ventricular function, patients with right ventricular involvement had worse left ventricular function and were more likely to have bilateral ventricular dysfunction compared with left ventricular involvement alone (67% vs. 8%, P <0.001) Scott W. Sharkey et al. reported 2019 [14-16]. Echocardiography may furtherly identify potential comorbidities of right ventricular TTS, such as mitral regurgitation, tricuspid regurgitation and intraventricular thrombosis [17,18].

For prognosis, some studies considered right ventricular involvement as an independent predictor of endpoint events [19], some studies considered right ventricular as an independent predictor of death [20-23] and some studies have suggested that right ventricular involvement has similar short-term and long-term endpoint event rates as left ventricular TTS alone [24-28]. Within our cases, 12-month follow-up was performed, one patient (22.2%)

died in the right ventricular affected TTS group, for other patients we set LVEF, Pulmonary Hypertension and the time of prognosis as criterions to assess prognosis. From our data it showed LVEF was lower for those patients with RV TTS at admission day, although after appropriate treatment, their LVEF back to almost normal when discharge from the hospital, usually 10 days at the average, for the long-term prognosis, the deterioration of LVEF would appear in the patients of RV TTS. The same process can be detected in the recovery of Pulmonary Hypertension, referred to (Figure 1 & 2). Therefore, longer time recovery needed and poor prognosis achieved for patients with RV TTS referred to (Figure 3).

## Discussion

### Major Findings

To our knowledge, this study is a small investigation of the comorbidities and prognostic impact of RV TTS. The study had 3 main findings: (1) patients with right ventricular involvement were more frequently older female, presented more commonly with typical TTS (apical ballooning), and with lower LVEF and higher BNP levels on admission; (2) Comorbidities such as Hydrothorax, Heart failure, Thrombus, Aneurysm, Mitral and tricuspid regurgitation (moderate or higher) could present in patients with RV TTS; (3) Extended recovery duration and higher mortality were associated with RV TTS followed up from discharge to 12-month. The results above are important in clinic as patients with those characteristics must be monitored closely after hospital admission, if identified earlier as RV TTS, which normally given the higher risk of potential clinical comorbidities, higher mortality and extended recovery, must be treated appropriately. In addition, patients with longer recovery duration were more likely to form ventricular thrombus which was found recently [29-34], because of the heavier myocardial injury and longer impairment of LV function [35-37]. Generally acknowledged, complicated and acute processes of the disease adversely impact the recovery rate [38-44], our patients went through prolonged recovery normally with higher level of Pulmonary artery pressure levels and lower level of LVEF supports this interpretation Schwarz et al recently reported [45]. It may just take more time to recover from a persistently high Pulmonary artery pressure and severely low LVEF than from a mild impairment of pump function.

### Study Limitations

This study is based on a single center registry, the department of cardiology, Affiliated Drum Tower Hospital, Medical School of Nanjing University from 2012 to 2018, the number of patients was small. Moreover, the dichotomous classification with or without right ventricular involvement may influence our results because of the unclear priori diagnostic criterion to diagnose RV TTS [37-39]. And the vast majority follow-ups were performed by echocardiography because cardiac magnetic resonance imaging was not performed in all patients for some objective reasons. Recovery estimates were assessed using Kaplan-Meier curves, given the retrospective limitation of assessing the exact time to recovery, however, multivariable covariates associated with the right ventricular involvement assessment of survival was not performed because of the limited number of events at follow-up, which may prevent to establish an accurate and reliable model.

## Conclusions

In summary, there are many differences between RV TTS and left ventricular involvement TTS alone. The current research and clinical data on RV TTS are basically derived from case reports and limited case studies, large-scale clinical data are lacking. Therefore, the epidemiology, pathogenesis, and prognosis of right ventricular involvement with or without RV TTS remain unclear, so there is no consistent diagnostic criterion. However, patients with the RV TTS, normally given the higher risk of potential clinical comorbidities, higher mortality and extended recovery, which should be treated appropriately in the early stage. What we need to do is strengthen both basic and clinical research on RV TTS meanwhile with the development and promotion of new technologies in regard to cardiac ultrasound, CMR and other imaging technology, in the future, to help developing RV TTS Patient management, reducing comorbidities events, and improving patient prognosis.

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