European Journal of Medical Research

RESEARCH

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Comparing outcomes of transcatheter tricuspid valve replacement and medical therapy for symptomatic severe tricuspid regurgitation: a retrospective study

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Abstract

Background Impaired hospitalizations for heart failure (HHF) and mortality are associated with tricuspid regurgitation (TR).

Objectives The objective of this study was to investigate the benefit of transcatheter tricuspid valve replacement (TTVR) over guideline-directed medical therapy (GDMT) in patients with symptomatic severe TR.

Methods Between May 2020 and April 2023, 88 patients with symptomatic severe TR were treated in our center. Of these, 57 patients received GDMT alone, and 31 patients underwent combined TTVR and GDMT. We collected and analyzed baseline data, and follow-up information for both groups. The primary endpoints were all-cause mortality and the combined endpoint (including all-cause mortality and HHF).

Results At a median follow-up of 20 (IQR 10–29) months, significant improvements were shown in TR severity, right ventricular function, and dimensions in TTVR group (all $P<0.001$). It also resulted in superior survival rates (75.8% vs. 48.4%, $P=0.019$), improved freedom from combined endpoint (61.5% vs. 45.9%, $P=0.007$) and fewer major adverse events. After stratification by TRI-SCORE, the subgroup with < 6 points in the TTVR group exhibited a significant difference in the combined endpoint compared to the other subgroups (all $P<0.05$), while no significant differences were observed in the GDMT subgroups ($P=0.680$).

Conclusions The utilization of LuX-Valve in TTVR effectively improves TR and is associated with lower rates of major adverse events, HHF and all-cause mortality. The TRI-SCORE may help identify higher-benefit patients with TR from TTVR.

Clinical trial registration ClinicalTrials.gov Protocol Registration System (NCT02917980).

Keywords Transcatheter tricuspid valve replacement, Guideline-directed medical therapy, Tricuspid regurgitation, TRI-SCORE, LuX-Valve

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Introduction

Tricuspid regurgitation (TR) is a prevalent condition often accompanied by congestive right heart failure, resulting in impaired symptoms [1, 2]. Although TR was previously considered benign, increased awareness reveals its association with excess mortality and poor long-term survival [1–3]. The progression of TR is influenced by numerous factors, with early-stage asymptomatic manifestations presenting a window for potential worsening of the condition. The prevalence of atrial fibrillation and left-sided heart valve disease in elderly patients accelerates tricuspid annulus dilation and worsening regurgitation [1–4]. This situation creates a vicious cycle in TR progression and causes repeat hospitalizations for heart failure (HHF), also emphasizing the consequences of inadequate management [1, 2, 5].

Under-treatment of severe TR is a significant concern due to historically high surgical mortality rates [6–9]. Additionally, patients with severe TR often face additional risk factors such as pulmonary hypertension and hepatorenal dysfunction, making them unsuitable for high-risk operations [7–10]. Consequently, clinical management of TR is conservative, with limited therapeutic options [11, 12].

Advancements in transcatheter techniques, including tricuspid-transcatheter edge-to-edge repair (T-TEER), have demonstrated the safety and effectiveness of treating severe TR to receive clinical benefit [13–17]. Transcatheter tricuspid valve replacement (TTVR) offers complete anatomical elimination of TR and shows promise in early clinical trials [18–20]. However, limited studies compare clinical outcomes between TTVR and guideline-directed medical therapy (GDMT). TRI-SCORE, a novel proposed risk stratification tool, is designed for indicating the surgical or interventional risk for patients with TR [21, 22]. Given the lack of randomized controlled trials, the study's objective was to examine the clinical characteristics of patients treated with TTVR and GDMT and to compare them to those of patients receiving GDMT alone in a single center. Additionally, we wanted to stratify the results based on the TRI-SCORE and evaluate the outcomes.

Materials and methods

Study population

This is a retrospective observational study in a single center. Between 1 May 2020 and 30 April 2023, a total of 126 patients were referred to this hospital for further treatment for diagnosed TR. Patients with mild, moderate, or asymptomatic TR [New York Heart Association (NYHA) functional class I] were excluded from the study. The eligibility of a patient for TTVR was assessed by a skilled multidisciplinary cardiac team. Concurrently, the patient receives GDMT to optimize their overall treatment plan.

The inclusion criteria for this study were as follows: (I) Age > 50 years old; (II) TR severity ≥ severe (3 +); (III) NYHA functional class ≥ II; (IV) High risk for TV surgery, as indicated by a Society of Thoracic Surgeons score > 8.0%. The exclusion criteria were: (I) Invasively systolic pulmonary arterial pressure measured by right heart catheterization > 60 mmHg (1 mm Hg = 0.133 kPa); (II) Left ventricular ejection fraction < 40%; and (III) Presence of other significant cardiac diseases (including other significant valvular heart disease, coronary heart disease or other structural heart disease) requiring additional interventional or surgical correction; (IV) Undergone left-sided valve surgery within the past 6 months or prior TV surgery. Additional inclusion criteria for TTVR group: (I) Suitable morphology for the safe implantation of the device in the position of TV as confirmed by computed tomography scan; and (II) Without jugular vein stenosis and an irregular shape, or without severe thoracic deformities.

The study was reviewed and approved by the Xijing Hospital Ethics Committee (KY20192138-C1), and all treatments administered to the patients adhered to the ethical guidelines outlined in the Declaration of Helsinki. All patients included in this study signed informed consent.

Data collection

Patients included in the study were identified through the outpatient electronic medical record system and the inpatient system. Comprehensive clinical characteristics, laboratory results, medication use, echocardiographic data, and major adverse events (MAE) were collected at baseline and during the follow-up period. The follow-up period commenced when the patients were initially referred or received TTVR and concluded either upon reaching the primary end point or upon study closure. For patients receiving GDMT alone, follow-up was conducted through outpatient visits or telephone communication. Patients who underwent TTVR in addition to GDMT were received comprehensive follow-up evaluations to one year after the procedure. Subsequently, they were regularly monitored through outpatient visits or via telephone communication. Additionally, information on time to and reason for hospitalization and cause and time of death was recorded after the patient received the targeted treatment.

The function and characteristics of the TV were indicated by quantifying the effective regurgitant orifice area and vena contracta width to help determine the efficacy of new transcatheter devices for patients with TR [23]. The severity of TR was assigned a grade of mild (1 +),

moderate (2+), severe (3+), massive (4+), or torrential (5+). Additionally, cardiac chamber sizes and functional parameters were quantified according to current recommendations and then collected [24].

Investigational devices and procedures

The TTVR procedures were successfully performed utilizing the dedicated devices the LuX-Valve system. As mentioned earlier, the LuX-Valve is distinguished by its unique design, which has demonstrated promising outcomes in preclinical studies. Additionally, the second-generation TTVR system, the LuX-Valve Plus, builds upon the shape and anchoring mechanism of the first-generation device. It can now be implanted via the transjugular approach, with the assistance of the new delivery system (33 Fr and 28 Fr), in anatomically suitable patients. Incorporating improvements, the tiptop of the LuX-Valve Plus can be flexed up to a maximum angle of 90°, optimizing the alignment of the stent with the tricuspid annulus. In comparison to the first-generation delivery system, this advancement effectively minimizes the risk of postoperative pulmonary complications and reduces trauma to the right chest and atrium [18, 20].

The TTVR procedure is conducted with the aid of transesophageal echocardiography and fluoroscopic guidance. The patient undergoing the procedure is placed under general anesthesia. The bioprostheses of the LuX-Valve are released through a delivery system that is carefully adjusted for optimal coaxiality and secured in place using septal anchoring and radial force-independent fixation. Technical success was defined as placement of the device in the position of the TV and the removal of the delivery system without life-threatening adverse events during the implantation. Procedural success was defined as the successful implantation of the device, the patient being alive at the end of the procedure, and a postprocedural TR grade of ≤ moderate (2+) (Fig. 1A).

Study end points

The primary end points of this study were all-cause mortality and the combined rate of HHF and all-cause mortality. Secondary end points included cardiovascular death, HHF, stroke, myocardial infarction, gastrointestinal bleeding, hepatic sclerosis, acute kidney injury, and renal failure requiring chronic replacement therapy. The definition of HHF was new-onset or worsening signs and symptoms of heart failure that required urgent therapy resulting in hospitalization. We also used the TRI-SCORE to partition and evaluate the outcomes of the combined end points in both treatment groups. The outcomes and complications were diagnosed and classified based on the updated Tricuspid Valve Academic Research Consortium document [25].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with 25th and 75th percentile. Within the treatment groups, comparisons were conducted using the Student's t-test or the Wilcoxon signed rank test. Between treatment groups, comparisons were made using the Student's t-test or the Mann–Whitney rank-sum test. Categorical variables are described as frequencies (%) and are compared using Fisher's exact test. Survival curves were constructed using Kaplan–Meier estimates and compared using log-rank statistics. The incidence per 100 person-years for complications during the follow-up period was calculated by dividing the number of new cases in the follow-up period by the total duration of follow-up for the entire group in years and then multiplying by 100. The 95% confidence interval for the incident rates was estimated using the Poisson distribution. Bilateral P values < 0.05 were considered statistically significant. R-Studio version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Results

Patient characteristics

Through systematic evaluation and screening, 88 patients with symptomatic severe TR met the criteria for this study and were included in the analysis. Fourteen patients with less than severe TR, 12 asymptomatic (NYHA functional class < III) patients and 12 patients with other significant cardiac symptoms requiring additional intervention were excluded from the study. Thirty-one cases met the suitability criteria and expressed willingness to undergo TTVR using the LuX-Valve. These patients also received concurrent GDMT as part of their treatment plan. A total of 57 patients were deemed ineligible or unwilling to undergo TTVR and were subsequently treated with GDMT alone. (Fig. 2).

Baseline clinical characteristics are presented in Table 1. At baseline, there were no significant differences in age, sex, and body mass index between the TTVR and GDMT groups. Both groups were identified as having a high surgical risk for TV surgery; however, it should be noted that the TTVR group faced higher risks compared to the GDMT group as indicated by the Society of Thoracic Surgeons score (11.0 ± 2.0 vs. 10.1 ± 1.0, $P = 0.011$) and the TRI-SCORE (6.9 ± 1.5 vs. 5.7 ± 1.6, $P < 0.001$). In the TTVR group, patients exhibited better quality of life measures, as evidenced by lower scores on the Kansas City Cardiomyopathy Questionnaire (34.7 ± 7.4 vs. 45.0 ± 5.2, $P < 0.001$). Additionally, a higher percentage of patients in the TTVR group were classified as NYHA III/IV (100% vs. 80.7%, $P < 0.001$), indicating

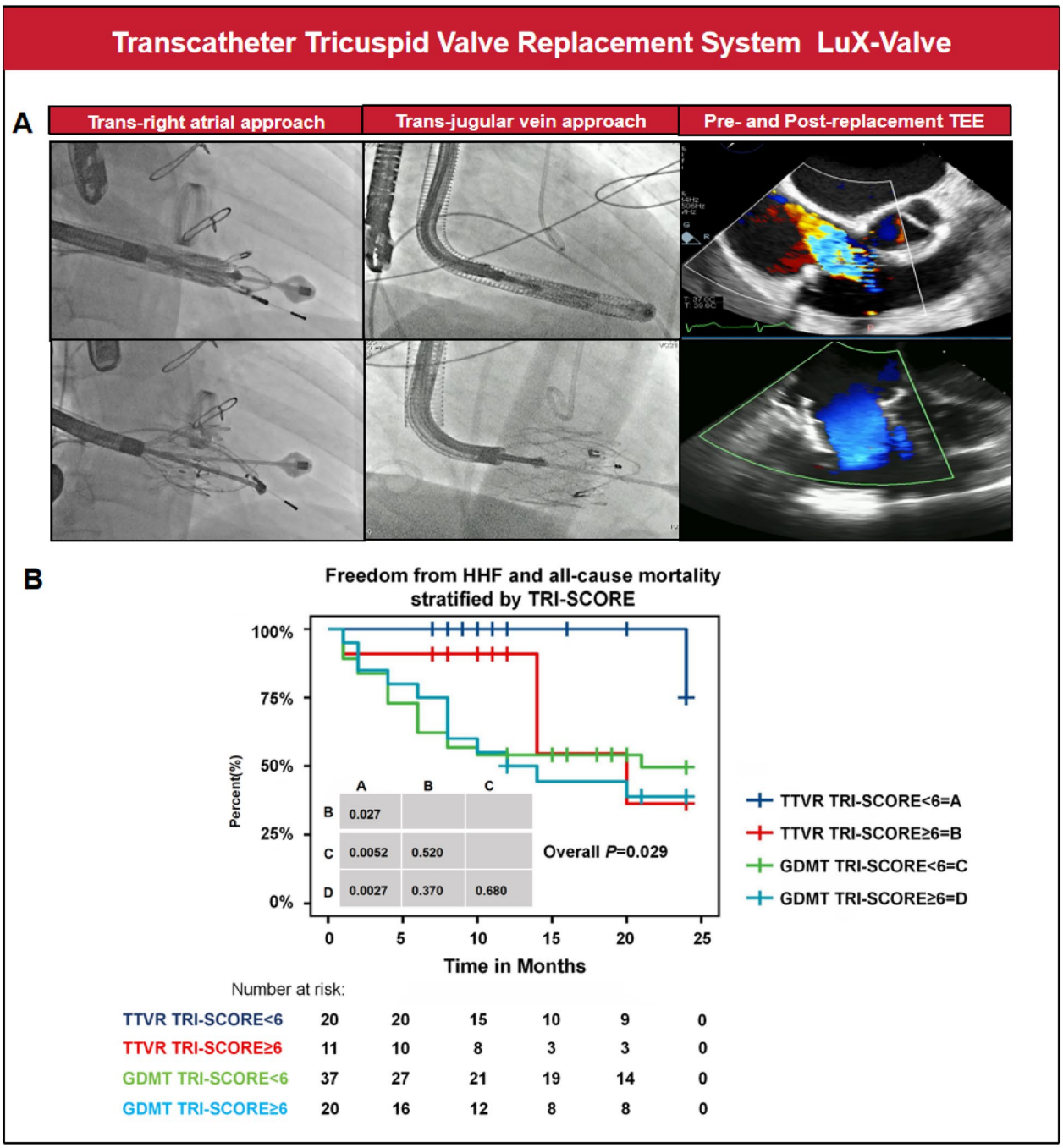

Fig. 1 The LuX-Valve systems and the transcatheter tricuspid valve replacement procedure. **A** Fluoroscopy images, pre- and post-replacement transesophageal echocardiography of LuX-Valve systems for transcatheter tricuspid valve replacement via the appropriate approaches. **B** Freedom from hospitalizations for heart failure and all-cause mortality stratified by TRI-SCORE. The numbers in the table are log-rank values between subgroups. GDMT, guideline-directed medical therapy; HHF, hospitalizations for heart failure; TEE, transesophageal echocardiography; TTVR, transcatheter tricuspid valve replacement

more severe symptoms. Additionally, laboratory tests showed worse renal (glomerular filtration rate), hepatic (aspartate transaminase), and cardiac function (N-terminal pro B-type natriuretic peptide) in the TTVR group ($P<0.001$). The utilization of medication usages was comparable between the two groups.

Baseline echocardiographic parameters are shown in Table 2. There was a notable disparity in the severity

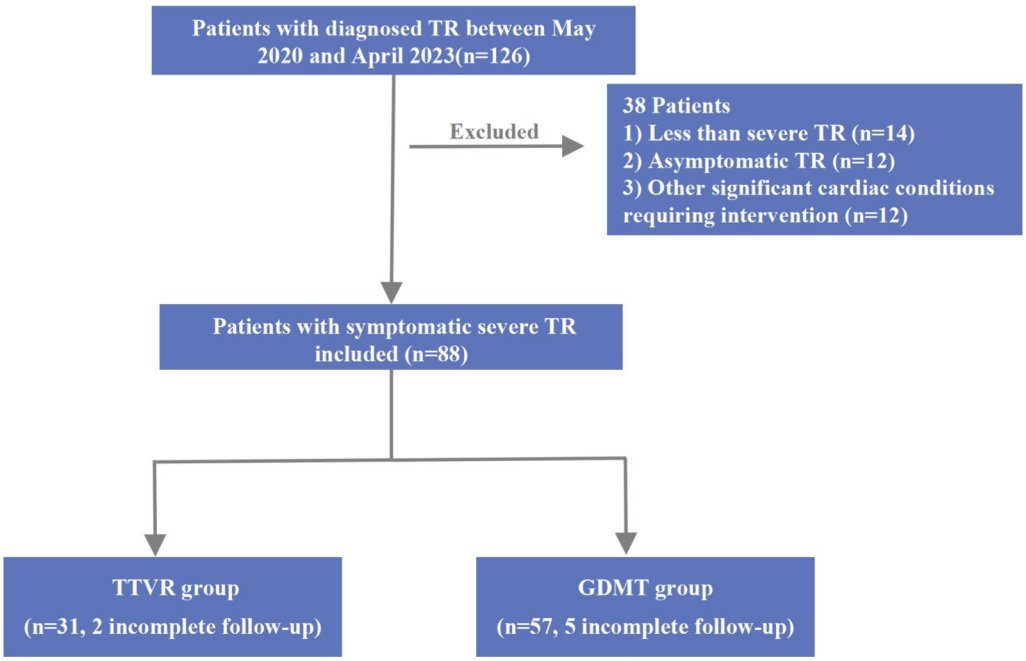

Fig. 2 A total of 88 patients with symptomatic severe tricuspid regurgitation were divided into the transcatheter tricuspid valve replacement group and guideline directed medical therapy group. GDMT, guideline directed medical therapy; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement

of baseline TR between the two groups. In the TTVR group, 20 patients (64.5%) had torrential TR, whereas in the GDMT group, 45 patients (78.9%) had severe TR ($P<0.001$). The TTVR group exhibited a greater right heart size compared to the GDMT group, as indicated by larger measurements of the right ventricle (RV) basal diameter (52.4 ± 9.1 mm vs. 47.0 ± 2.7 mm, $P<0.001$). Furthermore, the TTVR group demonstrated a more significant decline in RV function, as evidenced by lower measurements of tricuspid annular plane systolic excursion (14.3 ± 2.0 vs. 16.2 ± 2.1 mm, $P<0.001$).

Outcomes of TTVR

The TTVR procedure related outcomes are summarized in Table S1. Technical and procedural success were achieved in all the patients. A total of 31 patients underwent the TTVR procedure, with 15 patients receiving the procedure via the right atrium approach and 16 patients via the transjugular approach, as determined by preoperative assessment. One patient (3.2%) died during hospitalization due to lung infection and related to the procedure via the right atrium approach. Baseline, 30-day, and 6-month outcomes of TTVR are summarized in Table 3. Two patients in the TTVR group and five patients in the GDMT group had incomplete follow-up data. During the 6-month follow-up period, patients experienced enduring enhancements in the 6-min walk test (229.4 ± 64.6 mm vs. 355.3 ± 59.1 mm, $P<0.001$) and the Kansas City Cardiomyopathy Questionnaire (34.9 ± 7.4 vs. 58.3 ± 5.8, $P<0.001$). The severity of TR exhibited a significant reduction at the 30-day follow-up ($P<0.001$) and remained consistently improved at the 6-month follow-up. The patients with NYHA functional class I/II showed a substantial increase of 87% at the 6-month follow-up ($P<0.001$) (Fig. 3). At the 6-month follow-up, there was a significant decrease observed in the RV mid diameter (44.2 ± 5.0 mm vs. 37.2 ± 4.9 mm, $P<0.001$) as well as in the RA volume index (75.0 ± 8.2 mL/m^2 vs. 55.2 ± 2.7 mL/m^2, $P<0.001$). These findings suggest that the right heart undergoes reverse remodeling. The diameter of the inferior vena cava also showed a significant decrease from baseline ($P<0.001$). Significantly, these changes in cardiac dimensions were accompanied by a gradual improvement in right ventricular systolic function, as indicated by tricuspid annular plane systolic excursion (14.3 ± 2.0 mm vs. 16.4 ± 1.8 mm, $P<0.001$) (Fig. 4). It is, spironolactone, and other medications remained unchanged during the postoperative follow-up period.

Follow-up

In subsequent follow-up [median duration 12.0 (IQR 9.0–26.0) months for the TTVR group vs 19.0 (IQR 12.0–25.0) months for GDMT group, $P=0.362$], the TTVR

Table 1 Baseline characteristics

Variable	TTVR (N = 31)	GDMT (N = 57)	*P*-Value
Clinical			
Age (years)	66.4 ± 8.3	66.5 ± 6.9	0.97
Female n (%)	21 (67.7)	38 (66.7)	0.99
Body mass index (kg/m^2)	22.2 ± 2.3	22.5 ± 2.0	0.58
STS score (%)	11.0 ± 2.0	10.2 ± 1.0	**0.011**
TRI-SCORE points	6.9 ± 1.5	5.7 ± 1.6	**< 0.001**
≥ 6 points n (%)	11 (35.5)	20 (35.1)	0.99
6MWT (m)	229.4 ± 64.6	296.5 ± 67.7	**< 0.001**
KCCQ points	34.74 ± 7.4	45.0 ± 5.2	**< 0.001**
NYHA class n (%)			**< 0.001**
II	0 (0.0)	11 (19.3)	
III	13 (41.9)	38 (66.7)	
IV	18 (58.1)	8 (14.0)	
Total follow up duration-IQR (months)	12 (9.0–26.0)	19 (12.0–25.0)	0.36
Laboratory characteristics			
eGFR (mL/min/1.73m^2)	56.82 ± 11.9	66.0 ± 7.3	**< 0.001**
Creatinine (mmol/L)	124.50 ± 22.6	121.2 ± 23.4	0.90
Hemoglobin (g/L)	112.0 ± 16.8	113.2 ± 5.6	0.65
Alanine transaminase (U/L)	21.2 ± 6.2	24.0 ± 3.2	**0.006**
Aspartate transaminase (U/L)	30.0 ± 7.6	22.9 ± 4.4	**< 0.001**
NT-proBNP (pg/L)	1265.4 ± 608.7	923.8 ± 81.4	**< 0.001**
Medical history n (%)			
Peripheral edema	31 (100.0)	50 (87.7)	0.11
Ascites	15 (48.4)	22 (38.6)	0.51
Atrial fibrillation or flutter	28 (90.3)	48 (84.2)	0.62
Chronic obstructive pulmonary disease	14 (45.2)	12 (21.1)	**0.034**
Hypertension	23 (74.2)	41 (71.9)	0.99
Pulmonary hypertension[a]	18 (58.1)	38 (66.7)	0.57
Coronary artery disease	10 (32.3)	35 (61.4)	**0.017**
Prior stroke/TIA	4 (12.9)	10 (17.5)	0.79
Dyslipidemia or hyperlipidemia	20 (64.5)	40 (70.2)	0.76
Chronic kidney disease[b]	15 (48.4)	10 (17.5)	**0.005**
Severe liver disease[c]	11 (35.5)	6 (10.5)	**0.011**
Prior gastrointestinal hemorrhage	9 (29.0)	10 (17.5)	0.33
Left-sided valve surgery	21 (67.7)	27 (47.4)	0.11
PCI or CABG	8 (25.8)	22 (38.6)	0.33
CRT, PPM or ICD	9 (29.0)	10 (17.5)	0.33
Hospitalization for heart failure within 1 year before enrollment	16 (51.6)	23 (40.4)	0.43
Medications n (%)			
ACE-I, ARB, or ARNI	14 (45.2)	25 (43.9)	0.99
Loop diuretics	31 (100.0)	53 (93.0)	0.33
Spironolactone	22 (71.0)	32 (56.1)	0.26
β-receptor antagonist	21 (67.7)	41 (71.9)	0.87
Digitalis	6 (19.4)	19 (33.3)	0.25
Calcium channel blocker	6 (19.4)	13 (22.8)	0.92
Amiodarone	6 (19.4)	7 (12.3)	0.56

P < 0.05 denotes statistical significance and is presented in bold

Values are presented as mean ± standard deviation, median with interquartile range or n (%)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI angiotensin; CABG, coronary artery bypass graft; CRT cardiac resynchronization therapy, eGFR, estimated glomerular filtration rate; GDMT, guideline directed medical therapy; ICD implantable cardioverter–defibrillator; IQR,

Table 1 (continued)

interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; NT-proBNP, N-Terminal prohormone B-type natriuretic peptide; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack; TTVR, transcatheter tricuspid valve replacement; 6MWT, 6-min walk test

[a] Defined as pulmonary artery pressure ≥ 30 mm Hg

[b] Defined as eGFR < 60 mL/min

[c] Defined as MELD-albumin score > 12

Table 2 Baseline echocardiographic

Echocardiographic parameters	TTVR (N = 31)	GDMT (N = 57)	P-Value
TAPSE (mm)	14.3 ± 2.0	16.2 ± 2.1	**< 0.001**
RV-FAC (%)	35.2 ± 2.1	38.1 ± 2.9	**< 0.001**
RV systolic TDI (cm/s)	9.1 ± 1.2	10.2 ± 1.2	**< 0.001**
RVSP (mmHg)	42.3 ± 5.6	42.0 ± 5.0	0.76
RA volume index (mL/m^2)	75.0 ± 8.2	63.0 ± 6.1	**< 0.001**
VC width-biplane average (mm)	80.3 ± 5.3	77.3 ± 3.7	**0.003**
EROA by PISA (mm^2)	68.9 ± 6.3	58.9 ± 3.3	**< 0.001**
RV end-diastolic diameter base (mm)	52.4 ± 9.1	47.0 ± 2.7	**< 0.001**
RV end-diastolic diameter mid (mm)	44.2 ± 5.0	38.0 ± 4.7	**< 0.001**
TR volume (ml)	60.4 ± 8.1	52.7 ± 4.4	**< 0.001**
TR velocity (m/s)	3.0 ± 0.4	2.8 ± 0.3	**0.020**
TR etiology n (%)			0.68
Functional	21 (67.7)	40 (70.2)	
Organic	2 (6.5)	6 (10.5)	
Mixed	8 (25.8)	11 (19.3)	
TR severity n (%)			**< 0.001**
Severe	3 (9.7)	45 (78.9)	
Massive	8 (25.8)	9 (15.8)	
Torrential	20 (64.5)	3 (5.3)	
LVEDD (mm)	47.4 ± 9.1	43.0 ± 3.4	**0.002**
LVESD (mm)	34.5 ± 9.3	35.1 ± 4.3	0.71
LA volume index (mL/m^2)	74.8 ± 6.1	68.4 ± 12.3	**0.007**
LVEF (%)	53.9 ± 3.0	55.8 ± 4.3	**0.018**
Echo-sPAP (mm Hg)	45.3 ± 2.8	45.0 ± 3.9	0.68
IVC diameter (mm)	34.5 ± 1.8	30.3 ± 2.8	**< 0.001**

$P < 0.05$ denotes statistical significance and is presented in bold

Values are presented as mean ± standard deviation or n (%)

EROA, effective regurgitation orifice area; FAC, fractional area change; GDMT, guideline directed medical therapy; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; LVIDD, left ventricular internal dimension in diastole; LVIDS, left ventricular internal dimension in systole; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricular; RVSP, right ventricular systolic pressure; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue doppler imaging; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement;. VC, vena contracta

group had a significantly lower incidence per 100 person-years of follow-up of HHF [9.2, 95% confidence interval (CI) 4.2–17.5 vs 27.1, 95% CI 18.8–40.7, $P < 0.001$], gastrointestinal hemorrhage (6.9, 95% CI 2.5–15.0 vs 21.3, 95% CI 13.2–32.6, $P < 0.001$) and renal failure requiring dialysis (6.9, 95% CI 2.5–15.0 vs 16.9, 95% CI 9.7–27.4, $P < 0.001$) compared with GDMT group in follow-up (Table 4). The TTVR group had better 2-years survival (75.8% and 48.4%, $P = 0.019$) and freedom from 2-years combined endpoint (61.5% vs 45.9%, $P = 0.007$) compared with the GDMT group using Kaplan–Meier analysis. The rates of freedom from cardiovascular death exhibited no significant difference between TTVR and GDMT (78.3% vs. 57.1%; $P = 0.071$), whereas the rate of freedom from HHF showed a significant difference (71.5% vs. 52.4%; $P = 0.0039$) (Fig. 5). Furthermore, the analysis of freedom from the combined endpoint survival, stratified by the TRI-SCORE, is depicted in Fig. 1B (overall log-rank P = 0.029). The TTVR subgroup with a TRI-SCORE < 6 demonstrated the most favorable outcome, showing a significant difference compared to the other three subgroups (all inter-group differences $P < 0.05$). Irrespective of the stratified TRI-SCORE, GDMT did not exhibit superior efficacy in achieving the combined endpoint within the subgroups ($P = 0.680$).

Discussion

This study is a retrospective analysis conducted at a single center and focuses on patients with symptomatic severe TR. The findings of this study provide valuable insights into the management and treatment options for patients with symptomatic severe TR: (1) The combination of TTVR with GDMT demonstrated a co-benefit in terms of improved clinical outcomes and had lower rates of all-cause mortality and of combined HHF and all-cause mortality during follow-up compared to patients who received GDMT alone; (2) The LuX-Valve systems for TTVR have been proven to be safe and effective to reduce TR and to contribute to right heart reverse remodeling, functional restoration, and fewer MAE; and (3) The utilization of the TRI-SCORE for risk stratification allows for the identification of a patient population who is likely to receive more clinical benefit following TTVR.

Both study groups comprised patients with comorbidities and exhibited similarities in terms of age, systolic pulmonary arterial pressure, and the etiologic composition of TR. The primary inclusion criterion was the presence of symptomatic severe TR that was deemed appropriate for TTVR. To reduce potential bias and ensure that TR was the primary cause of severe symptoms, patients

Table 3 Patients' characteristics and medical therapy before and follow-up for TTVR

Patients' characteristics	Pre-TTVR	30 days	6 months	*P*- value	
	(N = 31)	(N = 30)	(N = 30)	a	b
6-MWT (m)	229.4 ± 64.6	287.1 ± 41.7	355.3 ± 59.1	**< 0.001**	**< 0.001**
KCCQ	34.9 ± 7.4	48.0 ± 7.3	58.3 ± 5.8	**< 0.001**	**< 0.001**
TAPSE (mm)	14.3 ± 2.0	15.1 ± 1.7	16.4 ± 1.8	0.08	**< 0.001**
RV-FAC (%)	35.6 ± 2.1	38.9 ± 3.7	41.1 ± 3.8	**< 0.001**	**< 0.001**
RV end-diastolic diameter base (mm)	52.4 ± 9.1	48.3 ± 5.4	43.2 ± 1.9	**0.039**	**< 0.001**
RV end-diastolic diameter mid (mm)	44.2 ± 5.0	40.7 ± 5.2	37.2 ± 4.9	**0.011**	**< 0.001**
RA volume index (mL/m^2)	75.0 ± 8.2	62.5 ± 5.2	55.2 ± 2.7	**< 0.001**	**< 0.001**
IVC diameter (mm)	34.5 ± 1.8	27.9 ± 2.1	24.5 ± 1.8	**< 0.001**	**< 0.001**
Medical therapy (mg/d)					
Loop diuretics	61.2 ± 9.2	64.9 ± 13.6	59.8 ± 14.4	0.22	0.65
Spironolactone	31.5 ± 9.6	28.7 ± 12.2	30.3 ± 10.0	0.32	0.65
ACE-I, ARB, or ARNI	445.2 ± 109.1	415.3 ± 104.6	396.7 ± 103.3	0.35	0.08
β-receptor antagonist	40.3 ± 8.0	39.8 ± 15.9	42.33 ± 7.7	0.87	0.32

P < 0.05 denotes statistical significance and is presented in bold

Values are presented as mean ± standard deviation

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI angiotensin receptor–neprilysin inhibitor; FAC, fractional area change; IVC, inferior vena cava; KCCQ, Kansas City Cardiomyopathy Questionnaire; RA, right atrium; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; 6MWT, 6-min walk test

a Student's t-test of baseline vs 30 days follow-up

b Student's t-test of baseline vs. 6-month follow-up

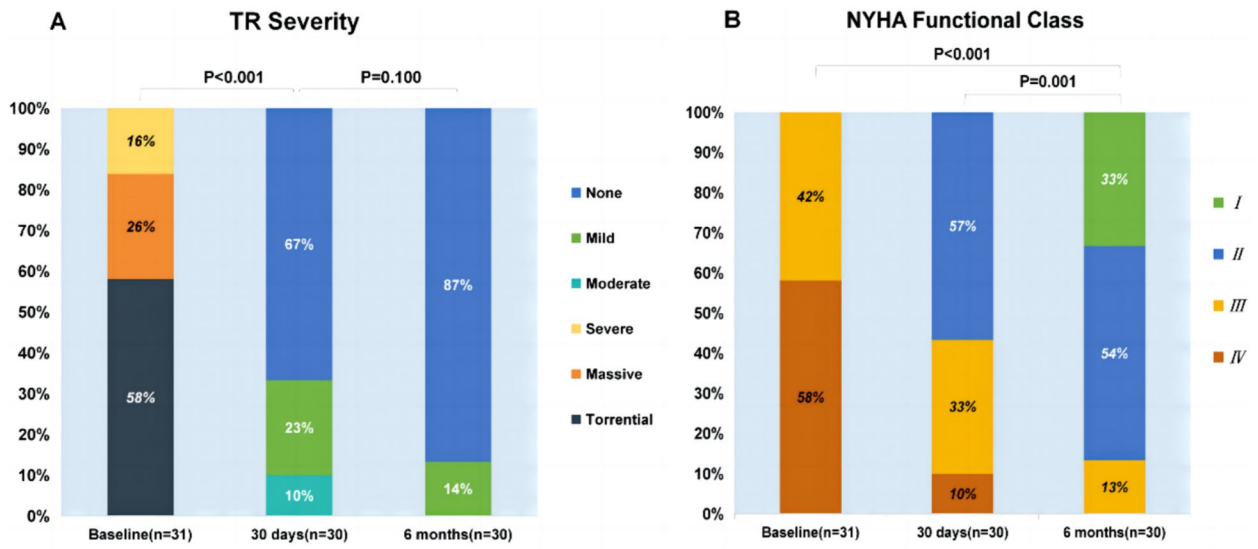

Fig. 3 Tricuspid regurgitation severity and New York Heart Association functional class at follow-up. **A** Tricuspid regurgitation reduction was observed with tricuspid regurgitation grade ≤ 2 + in 90% at 30 days and in 100% at 6 months. **B** Sustained New York Heart Association functional class improvement during the follow-up period. The proportion of patients classified as New York Heart Association functional class I/II increased to 87% at 6 months. The *P* values indicate significance calculated using the Fisher exact test. NYHA: New York Heart Association; TR: tricuspid regurgitation

with other severe cardiac conditions were excluded. The GDMT group demonstrated a mortality rate of 54% in the follow-up period, aligning with the estimated mortality rate associated with the natural history of TR [1, 2]. However, it is worth noting that at baseline, patients treated with TTVR exhibited a more pronounced symptom burden, lower quality of life, higher surgical risk, and a greater number of medical comorbidities compared to

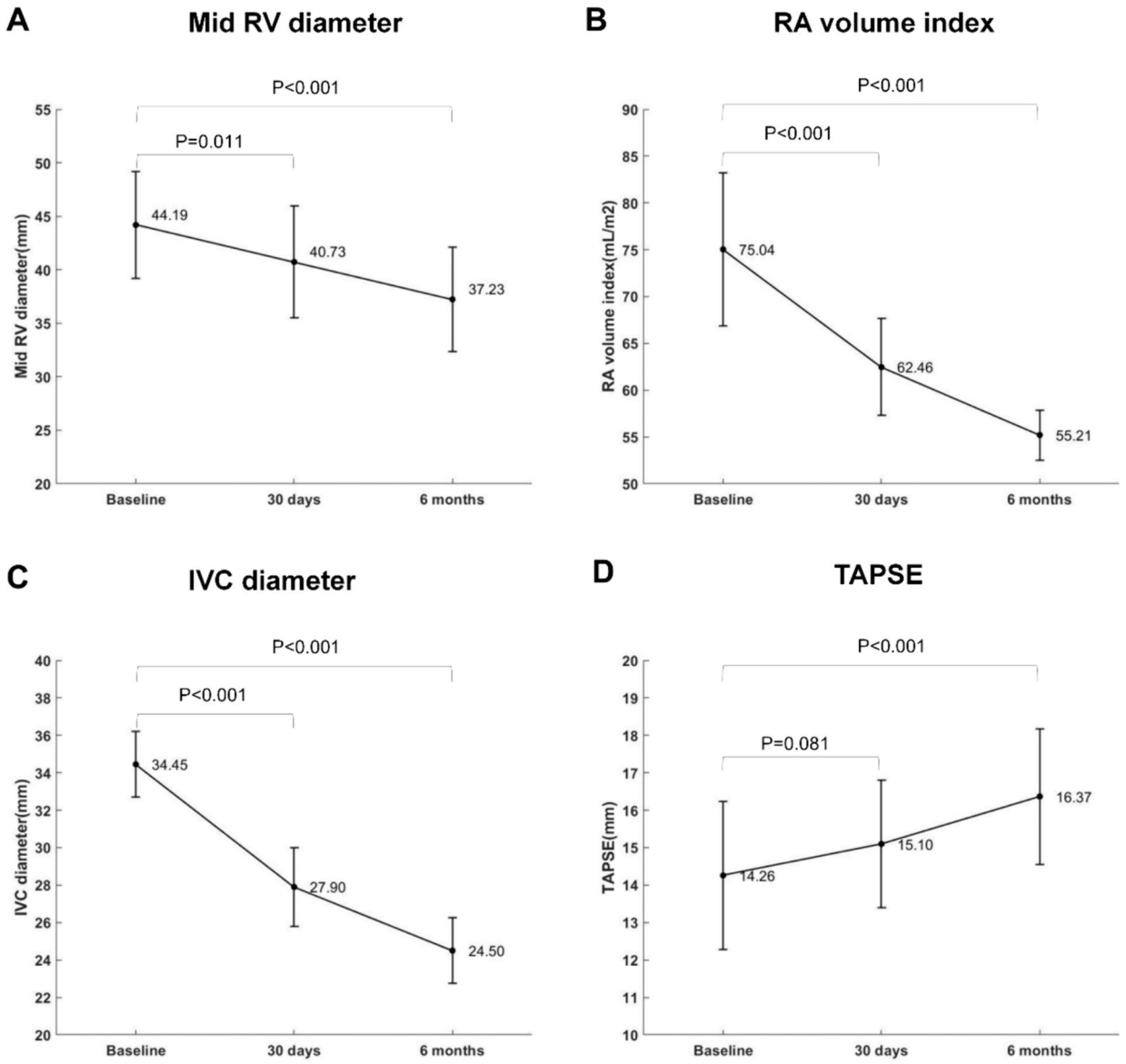

Fig. 4 Right heart reverse remodeling and functional recovery. Significant improvements in **A** right ventricular mid end-diastolic dimension; **B** right atrium volume index; and **C** systemic venous pressure were observed at the follow-up, indicating a positive physiological response to the reduction in tricuspid regurgitation reduction and the capacity for right heart reverse remodeling. There appears to be a trend for right ventricle systolic function recovery as indicated by **D** tricuspid annular plane systolic excursion. IVC, inferior vena cava; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion

those who received only GDMT. Despite these additional risk factors that can impact prognosis, TTVR using the LuX-Valve systems was associated with more favorable outcomes. Their feasibility and efficacy for TR have been demonstrated in previous studies. By showcasing positive outcomes and benefits, these studies have contributed to the growing body of knowledge on the effectiveness of TTVR in addressing severe TR [18, 20].

Correcting TR before the development of refractory right heart failure has been shown to improve RV function and induce reverse remodeling [1–4]. This intervention also prevents further enlargement of the annulus and secondary deterioration of tricuspid tethering [1, 3–5]. In the present study, TTVR led to a significant reduction in TR, with sustained effects observed over time. Furthermore, there was a trend toward reverse remodeling of the right heart, indicating a positive impact on the overall

Table 4 Follow-up major adverse events

Major adverse events	TTVR		GDMT		*P*-Value
	N = 31	Per 100 person-year (95% CI)	N = 57	Per 100 person-year (95% CI)	
Myocardial infarction	1(3.2)	2.3(0.3–8.3)	5(8.8)	2.2(0.3–7.9)	0.11
Stroke/TIA	0(0.0)	0	0(0.0)	0	0.99
Gastrointestinal hemorrhage	3(9.7)	6.9(2.5–15.0)	19(33.3)	21.3 (13.2–32.6)	**< 0.001**
Hepaticsclerosis	1(3.2)	4.6(1.3–11.8)	4(7.0)	4.5(1.2–11.5)	0.06
Acute kidney injury[a]	2(6.4)	2.3(0.8–8.3)	5(8.8)	2.2(0.3–7.9)	0.11
Renal failure requiring dialysis	3(9.6)	6.9(2.5–15.0)	15(26.3)	16.9(9.7–27.4)	**0.001**

P < 0.05 denotes statistical significance and is presented in bold

Values are presented as incidence per 100 person-year (95% CI)

CI, confidence interval; GDMT, guideline directed medical therapy; TTVR, transcatheter tricuspid valve replacement; TIA, transient ischemic attack

[a] Acute kidney injury: Increase in serum creatinine by 0.3 mg/dL or more (26.5 μmol/L or more) within 48 h; increase in serum creatinine to 1.5 times or more than the baseline of the prior 7 days; or urine volume less than 0.5 mL/kg/h for at least 6 h

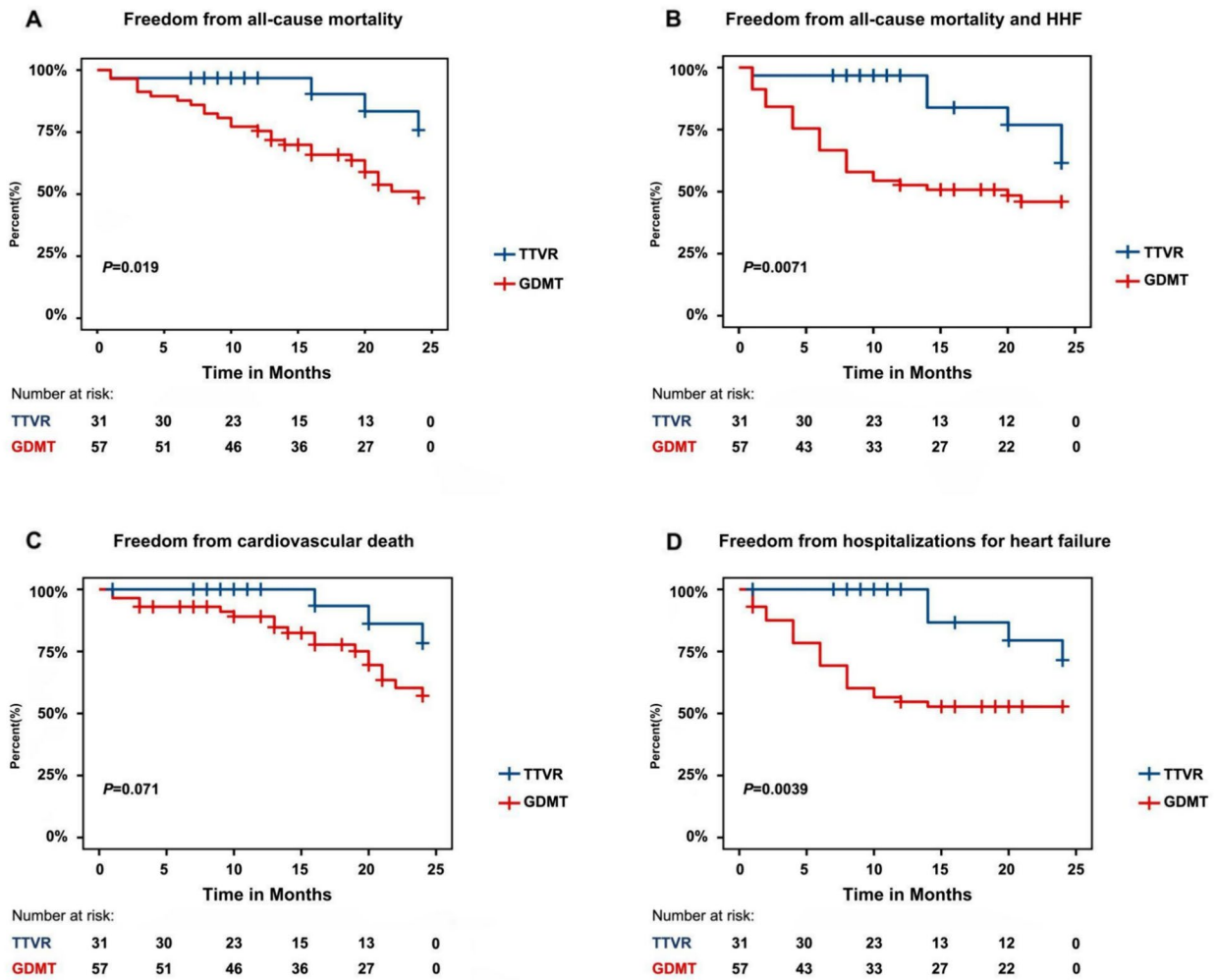

Fig. 5 Freedom from **A** all-cause mortality **B** combined hospitalizations for heart failure and all-cause mortality **C** cardiovascular death and **D** hospitalization for heart failure in the follow-up period. GDMT, guideline-directed medical therapy; HHF, hospitalizations for heart failure; TTVR, transcatheter tricuspid valve replacement

structure and function of the heart. These findings align with the conclusions of the TRILUMINATE trial and TRISCEND trial [17, 19]. Of note, in the results from the TRILUMINATE trial, there were no significant differences between T-TEER and GDMT in terms of all-cause mortality and HHF. Hence, when applying the results to guide clinical decision-making, consideration should also be given to the specific clinical setting and patient population in which they are implemented [26].

Furthermore, chronic congestion and fluid retention in the venous system can result in renal and hepatic damage, exacerbating these conditions. In fact, in cases of right heart failure, acute and chronic congestion can render up to 30% of patients resistant to diuretic treatment [1, 12, 27, 28]. Therefore, recalcitrant TR can develop, accompanied by irreversible RV dysfunction and ineffective response to medical therapy [1–3, 27–29]. This situation highlights the severity of the condition and the challenges in managing TR once it reaches an advanced stage [5–8]. The study findings within the GDMT group indicate that despite treatment, survival rates remained compromised and appeared unmodifiable. Additionally, a high proportion of adverse events, such as gastrointestinal hemorrhage and renal failure requiring dialysis, were observed during follow-up.

One of the major advantages of TTVR over T-TEER is the complete elimination of TR, which is particularly beneficial for patients with a high-pressure venous system, because it effectively alleviates prolonged congestive stasis in the liver and kidneys [11, 12, 29]. As a result, patients experience a more favorable clinical response to medical therapy. This fact highlights the significant impact of TTVR on improving the overall hemodynamic status and relieving the burden on vital organs [29]. During the follow-up period, we observed a notable decrease in the occurrence of MAE, including HHF, gastrointestinal hemorrhage, and renal failure requiring dialysis, in the TTVR group. This result suggests that TTVR synergized with GDMT has a positive impact not only on RV function but also on the overall clinical outcomes, reducing the incidence of these serious complications. These findings are also similar to the conclusions of studies regarding T-TEER conducted by Cai et al. [16] and Taramasso et al. [15]. Nonetheless, achieving total elimination of TR entails an abrupt shift in the RV preload and afterload, potentially leading to maladaptive responses in the renal, hepatic, and RV function, thereby inducing a dramatic deterioration in performance. In contrast to tricuspid TEER, this is an issue that demands meticulous scrutiny within the context of TTVR.

In our study, we introduced the TRI-SCOREas a risk assessment tool for the patients included. The TRI-SCORE allowed us to provide a reliable indication of the risk level associated with TR in these patients. Whereas the TRI-SCORE was primarily designed to predict in-hospital mortality following TR management [21, 22], our study also identified its predictive value for survival statues, despite the limited data available within the study cohort. For patient populations with a TRI-SCORE <6, TTVR can be utilized more confidently in clinical practice, because it is predicted to have a favorable prognosis. However, in patient populations with a TRI-SCORE ≥ 6, caution should be exercised when making decisions regarding the management in clinical, because individuals in this population may already be experiencing intractable right heart dysfunction as well as liver and kidney failure. In contrast, the TRI-SCORE did not show a significant predictive role for patients who received GDMT alone despite stratifying this group of patients based on risk using the TRI-SCORE. This finding does not necessarily imply limitations of the TRI-SCORE itself. It sheds light on the natural progression of TR and underscores the importance of early management of TR [1–3, 13–17].

Study limitations

This study also has several limitations. First, as this is a retrospective study, there exist baseline disparities between the two groups. Furthermore, the inclusion of patients who were not eligible for TTVR in the GDMT group, along with the absence of detailed follow-up data for these individuals, may potentially introduce bias into the interpretation of the results. To minimize bias, we excluded patients with worsening left heart function and other significant cardiac diseases during the selection process. However, these exclusion criteria may limit the generalizability of our findings [30, 31]. Second, TR can have multiple underlying causes that were not comprehensively considered in this study. At the time of enrollment, our focus was primarily on assessing the morphological suitability for safely implanting the device in the TV rather than addressing the specific underlying cause of valve disease. It is important to recognize that implementing TTVR to eliminate TR may not fully resolve the underlying cause of the valve disease. Last, patients' inclusion occurred during COVID-19 pandemic, and this might influence the all-cause mortality.

Conclusion

To the best of our knowledge, this is the first time that the clinical outcomes of patients who underwent TTVR versus GDMT for symptomatic severe TR have been compared and analyzed. TTVR using the LuX-Valve systems has produced significant improvements in functional status and quality of life associated with right-heart reverse remodeling, and has been

associated with lower rates of HHF and all-cause mortality. Furthermore, the TRI-SCORE as a dedicated risk stratification approach may provide valuable insights for guiding patients with TR toward and predicting patient survival.

Abbreviations

CI	Confidence interval
GDMT	Guideline-directed medical therapy
HHF	Hospitalizations for heart failure
MAE	Major adverse events
NYHA	New York Heart Association
RV	Right ventricle
T-TEER	Tricuspid Transcatheter edge-to-edge repair
TR	Tricuspid regurgitation
TTVR	Transcatheter tricuspid valve replacement
TV	Tricuspid valve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-01947-9.

Additional file 1.

Acknowledgements
None.

Author contributions
YW designed the study and interpreted the results; YW and YL were responsible for the data analyses and manuscript writing; XM and YL contributed to the results interpretation and discussion; MZ and PJ helped with data collection and pre-processing; FL and JY approved the manuscript submission. All authors read and approved the final manuscript.

Funding
This work was the Development and Transformation of New Technology and Construction of Precision Diagnosis and Treatment System for Transcatheter Interventional Diagnosis and Treatment of Structural Heart Diseases (2022YFC2503400), National Key Research and Development Programs (2022YFC2503402; 2020YFC2008100), and National Natural Science Foundation of China (82370375).

Availability of data and materials
The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by Clinicaltrials Organization: Xijing Hospital, Air Force Medical University (KY20192138-C1).

Consent for publication
Manuscript has been read and approved by all the authors for publication.

Competing interests
The authors have no competing of interest to declare.

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Received: 26 February 2024 Accepted: 23 June 2024
Published online: 05 August 2024

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