Characteristics and Outcomes In Patients With Left-Sided Infective Endocarditis Undergoing Left-Sided Valve Surgery With or Without Concomitant Tricuspid Annuloplasty

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Abstract

Background: In patients with left-sided infective endocarditis (LSIE) undergoing left-sided valve surgery (LVS), the effects of concomitant tricuspid annuloplasty (TA) on clinical features and prognosis remain unknown.

Methods: This is a single-center retrospective study conducted in a tertiary hospital in China. A total of 207 consecutive patients ≥ 18 years with a definite LSIE diagnosis who underwent LVS between 2008 and 2017 were included. Patients were divided into two groups: LVS alone ($n=157$) and LVS+TA group ($n=50$), to identify differences between the clinical features, echocardiographic parameters and outcomes.

Results: The mean age was 44.6 ± 15.6 years and 150 (72.5%) were male. Of the 207 patients, 71 (34.3%) patients had aortic valve involved alone, 115 (55.6%) had mitral valve involved alone and 21 (10.1%) had both valves involved. The average hospital stays were 38 ± 16 days and the median follow-up duration was 34.4 (IQR 19.8-56.3) months. Demographic and baseline characteristics were comparable between the two groups, except that the renal function in LVS alone group was better than LVS +TA group ($eGFR 97.2 \pm 28.8$ vs. 87.6 ± 30.7 , $P=0.046$). Significant reductions in left and right atrial diameter, left ventricular diameter, mitral and tricuspid regurgitation (TR) degree, and pulmonary arterial systolic pressure were reported in both groups, of which the differences were more prominent in LVS+ TA group than LVS alone group ($P<0.05$). The rate of postoperative complications was higher in LVS+ TA group than that in LVS group (44.0% vs. 23.6%, $P=0.005$). However, the in-hospital mortality and long-term mortality was similar in both groups. After multi-factor adjustment, concomitant TA was not significantly associated with in-hospital and long-term mortality.

Conclusions: Concomitant TA at the time of LVS significantly improved cardiac diameter but increased postoperative complications. It might not be associated with improved survival in LSIE patients.

Introduction

Despite the improvements in medical and surgical interventions, infective endocarditis remains a potentially lethal disease with the mortality ranging from 20–30% [1–4]. Early surgery significantly decreases the all-cause mortality and the incidence of embolic events in patients with left-sided infective endocarditis (LSIE) compared with conservative management, and it is recommended for patients meeting specific indications such as severe valve dysfunction [5–7]. As a prevalent condition, tricuspid regurgitation (TR) has attracted more and more discussions. Over 80% of tricuspid regurgitation is attributed to secondary (functional) causes including tricuspid annuli and right ventricle dilation, while primary causes account for less than 20% of TR. Functional TR is often secondary to left-sided heart disease, predominantly mitral valve disease [8–10]. For patients undergoing mitral-valve surgery, the rate of functional TR is up to 50% [11]. Recent study has revealed that increasing TR severity is correlated with worse prognosis regardless of left ventricular function or pulmonary hypertension, and severe TR may not predictably improve after left-sided valve surgery [6]. Nevertheless, concomitant tricuspid valve repair during left-sided valve surgery is beneficial from reducing cardiac-related mortality [12]. Consequently, the American valvular heart disease guideline recommends concomitant tricuspid annuloplasty (TA) for patients with severe TR undergoing left-sided valve surgery (LVS) [13]. However, there is a paucity of evidence available to define the benefit of concomitant TV surgery in patients with LSIE who need LVS. Most studies for the surgical management of functional TR are based on

rheumatic or degenerative valvular disease, while IE accounts for only 16% of the etiology of left-sided heart disease [14]. Unlike the chronic onset and presence of the latent phase in rheumatic or degenerative valvular disease, IE commonly presents with more acute onset and more aggressive progression due to different underlying pathophysiology. Thus, the previous evidence from rheumatic or degenerative valvular disease can hardly be extended to LSIE patients. In addition, most recommendations are categorized as Level of Evidence C, indicating the lack of high-quality trial or observational data. Therefore, our study aims to evaluate the effect of concomitant TA on clinical features and prognosis at the time of LVS among LSIE patients.

Methods

Study Population

This is a single-center retrospective observational study conducted in a tertiary referral hospital, the First Affiliated Hospital of Sun Yat-sen University. From January 1st of 2008 to September 30th of 2017, a total of 480 consecutive patients with clinical suspicion of IE were screened. We excluded patients who were younger than 18 years old (n=32), without definite IE (n=34) according to the modified Duke Criteria were included in the study [15], and without comprehensive echocardiographic evidence of endocarditis (n=32). Patients with evidence of right-sided endocarditis (n=37), cardiac implantable electronic devices (pacemakers and implantable cardioverter-defibrillators) (n=4), both-sided IE (n=11), and congenital heart disease-related IE (n=21) were also excluded, given these subtypes have completely distinct clinical, microbiological, and prognostic characteristics from LSIE. We also excluded 102 patients who didn't undergo IE surgery. Finally, a total of 207 patients ≥ 18 years old with a definite LSIE diagnosis undergoing LVS were included in the study (**Figure 1**). Patients were further divided into two groups depending on the type of definitive interventions they received: LVS group (n=157), and LVS+TA group (n=50). The LVS group conducted left-sided valve surgery alone, while the LVS+ TA group underwent concomitant TA with LVS.

Definition of terms

The estimated glomerular filtration ratio (eGFR) was calculated using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine (eGFR_{cr}) equation [16]. The presence of heart failure was determined by symptoms and signs elicited from clinical assessment, laboratory investigations, and radiographic findings at baseline preoperatively [17, 18]. Systemic embolisms were defined as acute onset of clinical symptoms or signs indicating a lodging embolus involving the brain, spleen, kidneys, or lung, consistent with radiographic evidence [19]. Vascular phenomena, such as cutaneous microinfarctions and metastatic abscesses, were not classified under systemic embolisms. Neurological complications included meningoencephalopathies, ischemic complications, cerebral hemorrhage, and intracranial abscess [20]. According to previous studies and guidelines, paravalvular complications were defined as intracardiac abscesses or fistulas based on transthoracic or transesophageal echocardiograms [21, 22]. Postoperative complications included major bleeding, neurological complications, cardiac complications, infection, and thoracic effusion or pneumothorax and poor wound healing. Major bleeding was defined as: 1) intracranial bleeding; 2) overt bleeding resulting in a decrease in hemoglobin ≥ 20 g/L or requiring blood transfusion; or 3) bleeding into a confined space, such as pericardial cavity or paraspinal space, which indicates severe morbidity. The definition of neurological complications was above-mentioned. Cardiac complications

included heart failure, arrhythmia, massive pericardial effusion, and low cardiac output syndrome. The study outcome for this analysis was in-hospital and long-term all-cause mortality. Since the high in-hospital mortality rate, the long-term all-cause mortality was calculated from both index admission and from discharge respectively.

Data collection and measurement of echocardiographic parameters

Baseline data were collected from the electronic medical record system, including the patients' demographic characteristics, previous history of underlying diseases, clinical presentations, laboratory test results on admission, transthoracic/transesophageal echocardiographic data, complications and microscopic studies of associated pathogens. The clinical severities were assessed by the Pitt bacteremia scores (PBS) ranging from 0 to 14 points with the higher score indicating the severer status [23].

Transthoracic echocardiograms (TTE) were performed at baseline preoperatively and postoperatively. The median duration of postoperative TTE performed were 8 (inter-quartile range, IQR: 7-13) days post operation. Left ventricular ejection fraction (LVEF) was measured by Simpson's method. In accordance of the recommendations from American Society of Echocardiography, the severity of tricuspid regurgitation was assessed using color Doppler flow images in TTE and graded qualitatively as mild (1+), moderate (2+), or severe (3+ or 4+) following the jet area-central jets of < 5, 5- 10, or > 10 cm² respectively [24]. The pulmonary artery systolic pressure was calculated as the addition of estimated right atrial pressure (ranging from 5 to 10 mmHg given the varied size of inferior vena cava) and the systolic right atrial-ventricular pressure gradient (PG/ ΔP), which was calculated by the modified Bernoulli equation: $\Delta P = 4 \times v^2$ (v: the maximal velocity of the TR jet area) [25].

Surgery procedures

All operations were performed under conventional cardiopulmonary bypass, mild or moderate hypothermia through median sternotomy. Mitral or aortic valve surgeries were performed before examining the tricuspid valve. For patients who underwent concomitant TA, either De Vega annuloplasty or ring annuloplasty were used according to the surgeon's comprehensive evaluations following the latest guidelines' recommendations at that time [26-28].

Statistical Analysis

Continuous normally distributed variables were described as mean value with standard deviation (SD) or median (IQR) when appropriate. For quantitative variables, the groups were compared by a two-tailed Student's t-test or Mann-Whitney U-test when necessary. Categorical variables were expressed as number of event and a percentage, and they were examined by the χ^2 test or Fisher's exact test when appropriate. Categorical echocardiographic variables change between pre- and post-operation were analyzed using McNemar's statistical test.

Multivariable logistic regression models were applied to determine whether concomitant TA were associated with in-hospital mortality postoperation after adjusting for confounding factors. Multivariable cox regression models were used to explore the association of concomitant TA with long-term survival adjusted for

predefined covariates. The survival time was calculated from death or the last time of follow up to hospital discharge. Since the high rate of in-hospital mortality, the survival time between death or last time of follow up to hospital admission were also discussed.

All hypothesis tests were two-sided, and a P value < 0.05 was considered as statistically significant. Statistical analysis was performed with SPSS software V22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics of Patients

The baseline characteristics of the overall study population were demonstrated in **Table 1**. The mean age was 44.6 ± 15.6 years and 150 (72.5%) were male. 97.1% of the cohort were native IE patients, while only 2.9% were prosthetic IE patients. 71 (34.3%) of patients had aortic valve involved alone, 115 (55.6%) had mitral valve involved while 21 (10.1%) had both aortic and mitral valves involved. A total of 157 (75.8%) patients underwent LVS alone while 50 (24.2%) underwent concomitant TA. Of the 50 patients underwent concomitant TA, 18 (36.0%) received De Vega annuloplasty while 32 (54.0%) received ring annuloplasty.

Table 1
Baseline Characteristics of Patients with LSIE

Variables	All (n = 207)	LVS (n = 157)	LVS + TA (n = 50)	<i>P</i> value
Age (yrs)	44.6 ± 15.6	44.0 ± 15.7	46.2 ± 15.1	0.388
Male, n (%)	150 (72.5)	110 (71.0)	40 (80.0)	0.171
Atrial fibrillation, n (%)	18 (8.7)	10 (6.4)	8 (16.0)	0.035
Hypertension, n (%)	37 (17.9)	29 (18.5)	8 (16.0)	0.691
Diabetes mellitus, n (%)	10 (4.8)	9 (5.7)	1 (2.0)	0.284
Coronary artery disease, n (%)	16 (7.7)	12 (7.6)	4 (8.0)	0.934
Rheumatic heart disease, n (%)	31 (15.0)	22 (14.0)	9 (18.0)	0.491
COPD, n (%)	3 (1.4)	2 (1.3)	1 (2.0)	0.708
Chronic kidney disease, n (%)	18 (8.7)	16 (10.2)	2 (4.0)	0.176
NYHA class, n (%)				0.712
Class I	14 (6.8)	12 (7.6)	2 (4.0)	
Class II	68 (32.9)	52 (33.1)	16 (32.0)	
Class III	109 (52.7)	80 (51.0)	29 (58.0)	
Class IV	16 (7.7)	13 (8.3)	3 (6.0)	
Serum creatine (mg/dl)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.9 (0.8–1.3)	0.019
eGFR (ml/min/1.73m ²)	94.9 ± 29.5	97.2 ± 28.8	87.6 ± 30.7	0.046
Types of IE, n (%)				0.133
Left-sided native IE	201 (97.1)	154 (98.1)	47 (94.0)	
Left-sided prosthetic IE	6 (2.9)	3 (1.9)	3 (6.0)	
Valve involved, n (%)				
Aortic	71 (34.3)	55 (35.0)	16 (32.0)	0.728
Mitral	115 (55.6)	85 (54.1)	30 (60.0)	
Aortic and mitral	21 (10.1)	17 (10.8)	4 (8.0)	

IE, infective endocarditis; LSIE, left-sided infective endocarditis; LVS, left-sided valve surgery only; TA, tricuspid annuloplasty; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty; COPD, chronic obstructive pulmonary disease; NYHA, New York heart association; eGFR, estimated glomerular filtration rate derived from serum creatinine according to CKD-EPI.

*Of the 32 patients with negative cultures, 12 of 24 (54.5%) in the LVS group and 3 of 10 (30.0%) in the LVS + TA group had a history of antibiotic use.

Variables	All (n = 207)	LVS (n = 157)	LVS + TA (n = 50)	<i>P value</i>
Causative microorganism, n (%)				0.195
Streptococcus	61 (29.5)	52 (33.1)	9 (18.0)	
Staphylococcus aureus	10 (4.8)	8 (5.1)	2 (4.0)	
Others	104 (50.2)	75 (47.8)	29 (58.0)	
Negative culture*	32 (15.5)	22 (14.0)	10 (20.0)	
Pitt score, IQR	1.0 (0–2.0)	1.0 (0–3.0)	1.0 (0–2.0)	0.134
IE, infective endocarditis; LSIE, left-sided infective endocarditis; LVS, left-sided valve surgery only; TA, tricuspid annuloplasty; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty; COPD, chronic obstructive pulmonary disease; NYHA, New York heart association; eGFR, estimated glomerular filtration rate derived from serum creatinine according to CKD-EPI.				
*Of the 32 patients with negative cultures, 12 of 24 (54.5%) in the LVS group and 3 of 10 (30.0%) in the LVS + TA group had a history of antibiotic use.				

Demographic and baseline characteristics were comparable between the two groups, except that patients undergoing LVS with concomitant TA had significantly higher rate of atrial fibrillation (16.0% vs. 6.4%, $P = 0.035$) and worse renal function than those without TA (eGFR 87.6 ± 30.7 vs 97.2 ± 28.8 , $P = 0.046$). The Pitt bacteremia scores were comparable between the two groups ($P = 0.134$).

Echocardiographic characteristics

A comparison of echocardiographic characteristics among patients undergoing left-sided surgery with or without concomitant TA was presented in **Table 2**. At baseline, the LVS + TA group had greater left atrial diameter (LA), right atrial diameter (RA), right ventricular diameter (RV), more severe mitral regurgitation (MR) and TR, higher PASP as well as larger vegetations compared with LVS group ($P < 0.05$).

Table 2

Echocardiographic results pre-operation and post-operation in patients undergoing left-sided valve surgery with or without concomitant tricuspid annuloplasty (TA).

Variables	All (n = 207)	LVS (n = 157)			LVS + TA (n = 50)			P value*
		Pre- operation	Post- operation	$\Delta \pm$ SD	Pre- operation	Post- operation	$\Delta \pm$ SD	
LA (mm)	42.7 $\pm$ 9.0	40.7 $\pm$ 8.0	34.3 $\pm$ 6.6 [#]	-6.2 $\pm$ 7.1	47.8 $\pm$ 9.0 [†]	39.4 $\pm$ 7.6 [#]	-8.8 $\pm$ 8.2	0.040
RA_LAD (mm)	46.3 $\pm$ 7.7	44.8 $\pm$ 7.2	41.9 $\pm$ 7.3 [#]	-2.9 $\pm$ 5.6	51.1 $\pm$ 7.4 [†]	41.7 $\pm$ 7.2 [#]	-8.6 $\pm$ 8.6	< 0.001
RA_SAD (mm)	35.8 $\pm$ 6.6	34.7 $\pm$ 6.2	35.7 $\pm$ 5.8	+0.8 $\pm$ 4.9	39.1 $\pm$ 6.9 [†]	36.8 $\pm$ 5.9	-2.3 $\pm$ 7.1	0.001
LVEDD (mm)	57.6 $\pm$ 10.2	57.5 $\pm$ 9.0	45.4 $\pm$ 7.7 [#]	-11.8 $\pm$ 7.5	58.1 $\pm$ 13.5	48.0 $\pm$ 10.9 [#]	-10.1 $\pm$ 14.9	0.324
LVESD (mm)	36.1 $\pm$ 7.4	35.7 $\pm$ 6.9	31.7 $\pm$ 6.6 [#]	-3.8 $\pm$ 5.6	37.2 $\pm$ 8.6	34.5 $\pm$ 8.4 [#]	-3.3 $\pm$ 7.2	0.701
RV (mm)	20.9 $\pm$ 4.4	20.4 $\pm$ 4.1	19.7 $\pm$ 3.4	-0.6 $\pm$ 4.7	22.5 $\pm$ 5.2 [†]	22.1 $\pm$ 3.7	-0.4 $\pm$ 5.6	0.772
IVS (mm)	10.3 $\pm$ 2.3	10.2 $\pm$ 2.1	11.0 $\pm$ 2.8 [#]	+0.8 $\pm$ 2.7	10.5 $\pm$ 3.1	12.2 $\pm$ 5.7 [#]	+1.6 $\pm$ 5.4	0.188
LVPW (mm)	9.4 $\pm$ 1.9	9.3 $\pm$ 1.7	10.1 $\pm$ 2.5 [#]	+0.8 $\pm$ 2.7	9.5 $\pm$ 2.3	11.0 $\pm$ 4.9	+1.3 $\pm$ 4.6	0.369
EF (%)	66.7 $\pm$ 8.5	67.0 $\pm$ 8.7	60.0 $\pm$ 9.2 [#]	-7.6 $\pm$ 10.4	66.2 $\pm$ 8.0	58.5 $\pm$ 12.0 [#]	-7.4 $\pm$ 12.2	0.937
E/A ratio	1.4 $\pm$ 0.8	1.4 $\pm$ 0.7	1.0 $\pm$ 0.5 [#]	-0.5 $\pm$ 1.0	1.7 $\pm$ 0.9	1.2 $\pm$ 0.4 [#]	-1.0 $\pm$ 2.7	0.602
E/E' ratio	12.4 $\pm$ 5.5	11.5 $\pm$ 5.7	14.0 $\pm$ 6.1	+3.4 $\pm$ 7.3	14.3 $\pm$ 4.6	14.0 $\pm$ 1.1	+3.7 $\pm$ 5.1	0.963

LVS, left-sided valve surgery only; TA, tricuspid annuloplasty; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty; EF, ejection fraction; LA, left atrial; RA_LAD, right atrial long axis diameter; RA_SAD, right atrial short axis diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RV, right ventricular; IVS, interventricular septum; LVPW, left ventricular posterior wall; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; MR, mitral regurgitation; PR, pulmonary regurgitation; AR, aortic regurgitation; CTR, chordae tendineae rupture.

* P < 0.05 for the echocardiographic changes (Δ) between LVS and LVS + TA group.

† P < 0.05 versus LVS group preoperation.

P < 0.05 postoperation versus preoperation.

Variables	All (n = 207)	LVS (n = 157)			LVS + TA (n = 50)			P value*
		Pre- operation	Post- operation	$\Delta \pm$ SD	Pre- operation	Post- operation	$\Delta \pm$ SD	
Diastolic dysfunction, n (%)	68 (32.9)	51 (32.5)	30 (19.1)	-10.8%	17 (34.0)	9 (18.0)	-16.0%	
PASP (mmHg)	44.9 $\pm$ 15.2	41.9 $\pm$ 13.9	30.6 $\pm$ 8.3 [#]	-9.2 $\pm$ 13.6	51.4 $\pm$ 16.3 [†]	29.6 $\pm$ 6.7 [#]	-24.1 $\pm$ 16.8	< 0.001
TR	1.18 $\pm$ 0.58	1.04 $\pm$ 0.48	0.94 $\pm$ 0.33 [#]	-0.10 $\pm$ 0.54	1.64 $\pm$ 0.63 [†]	0.94 $\pm$ 0.24 [#]	-0.70 $\pm$ 0.68	< 0.001
MR	2.18 $\pm$ 0.90	2.11 $\pm$ 0.92	0.58 $\pm$ 0.53 [#]	-1.54 $\pm$ 1.02	2.40 $\pm$ 0.78 [†]	0.50 $\pm$ 0.51 [#]	-1.90 $\pm$ 1.04	0.030
PR	0.86 $\pm$ 0.48	0.87 $\pm$ 0.45	0.80 $\pm$ 0.40	-0.06 $\pm$ 0.51	0.86 $\pm$ 0.57	0.88 $\pm$ 0.33	-0.02 $\pm$ 0.59	0.335
AR	1.29 $\pm$ 1.24	1.30 $\pm$ 1.25	0.42 $\pm$ 0.50 [#]	-0.88 $\pm$ 1.05	1.28 $\pm$ 1.25	0.38 $\pm$ 0.64 [#]	-0.90 $\pm$ 1.16	0.905
TR < moderate, n (%)	158 (76.3)	136(86.6)	137 (87.3)	+ 0.7%	22 (44.0) [†]	50 (100)	+ 56.0%	-
MR < moderate, n (%)	53 (25.6)	44 (28.0)	141 (89.8)	+ 61.8%	9 (18.0)	50 (100)	+ 82.0%	-
PR < moderate, n (%)	197 (95.2)	150 (95.5)	141 (89.8)	-0.7%	47 (94.0)	50 (100)	+ 6.0%	-
AR < moderate, n (%)	120 (58.0)	89 (56.7)	142 (90.4)	+ 33.7%	31 (62.0)	48 (96.0)	+ 34.0%	-

LVS, left-sided valve surgery only; TA, tricuspid annuloplasty; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty; EF, ejection fraction; LA, left atrial; RA_LAD, right atrial long axis diameter; RA_SAD, right atrial short axis diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RV, right ventricular; IVS, interventricular septum; LVPW, left ventricular posterior wall; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; MR, mitral regurgitation; PR, pulmonary regurgitation; AR, aortic regurgitation; CTR, chordae tendineae rupture.

* P < 0.05 for the echocardiographic changes (Δ) between LVS and LVS + TA group.

† P < 0.05 versus LVS group preoperation.

P < 0.05 postoperation versus preoperation.

Variables	All (n = 207)	LVS (n = 157)			LVS + TA (n = 50)			<i>P</i> value*
		Pre- operation	Post- operation	$\Delta \pm$ SD	Pre- operation	Post- operation	$\Delta \pm$ SD	
Vegetation size (mm)	12.5 $\pm$ 6.1	11.7 $\pm$ 5.6	-	-	15.0 $\pm$ 6.9†	-	-	-
Vegetation > 10mm	88 (42.5)	60 (38.2)	-	-	28 (56.0)	-	-	-
Vegetation > 15mm	48 (23.2)	32 (20.4)	-	-	16 (32.0)	-	-	-
CTR, n (%)	45 (21.7)	35 (22.3)	0	-	10 (20.0)	0	-	-
Paravalvular complications, n (%)	61 (29.5)	45 (28.1)	0	-	18 (36.0)	0	-	-
LVS, left-sided valve surgery only; TA, tricuspid annuloplasty; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty; EF, ejection fraction; LA, left atrial; RA_LAD, right atrial long axis diameter; RA_SAD, right atrial short axis diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RV, right ventricular; IVS, interventricular septum; LVPW, left ventricular posterior wall; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; MR, mitral regurgitation; PR, pulmonary regurgitation; AR, aortic regurgitation; CTR, chordae tendineae rupture.								
* P < 0.05 for the echocardiographic changes (Δ) between LVS and LVS + TA group.								
† P < 0.05 versus LVS group preoperation.								
# P < 0.05 postoperation versus preoperation.								

After surgical intervention, both the LVS group and the LVS + TA group manifested smaller cardiac chambers and alleviated valvular regurgitation. LVEF was decreased in both groups, indicating possible transient deterioration in cardiac function after surgery. However, the postoperative reductions of LA and RA diameter, MR and TR severity, as well as PASP were more significant in the LVS + TA group than in the LVS group ($P < 0.05$), implying the superiority of concomitant TA in improving echocardiographic parameters.

Complications and outcomes

Stratified by surgical interventions with or without concomitant TA, the complications, surgical treatment and outcomes were summarized in **Table 3**. Of the 207 patients on admission, presentations of heart failure, systemic embolisms, neurological complications, and metastatic infection were 48 (23.2%), 37 (17.9%), 41 (19.8%) and 26 (12.6%) respectively. There was no evidence of significant differences in preoperative complications between the two treatment groups ($P > 0.05$). Of the 207 patients, a large proportion of patients underwent valve replacement instead of valvuloplasty (97.6% vs. 2.4%). The LVS + TA group presented with significantly increased operation time (326 ± 111 vs. 278 ± 95 mins, $P = 0.003$) and postoperative complications rate compared with LVS group (44.0% vs. 23.6%, $P = 0.005$).

Table 3

Complications, Surgical treatment and Outcomes of the Patients with LSIE Stratified by Surgery Type.

Variables	All (n = 207)	LVS (n = 157)	LVS + TA (n = 50)	<i>P value</i>
IE complications preoperation, n (%)				
Heart failure	48 (23.2)	35 (22.3)	13 (26.0)	0.589
Systemic embolism	37 (17.9)	31 (19.7)	6 (12.0)	0.213
Neurologic complications	41 (19.8)	31 (19.7)	10 (20.0)	0.969
Metastatic infection	26 (12.6)	16 (10.2)	10 (20.0)	0.068
Left-sided valve surgery, n (%)				
Valvuloplasty	5 (2.4)	5 (3.2)	0	0.201
Valve replacement	202 (97.6)	152 (96.8)	50 (100)	
Types of valve replaced, n (%)				
Mechanical valve	156 (77.2)	114 (75.0)	42 (84.0)	0.188
Biological valve	46 (22.8)	38 (25.0)	8 (16.0)	
Postoperative complications, n (%)	59 (28.5)	37 (23.6)	22 (44.0)	0.005
Major Bleeding	21 (10.1)	13 (8.3)	8 (16.0)	0.115
Neurological complications	6 (2.9)	4 (2.5)	2 (4.0)	0.594
Cardiac complications	24 (11.6)	15 (9.6)	9 (18.0)	0.104
Infection	10 (4.8)	8 (5.1)	2 (4.0)	0.753
Thoracic effusion or pneumothorax	7 (3.4)	5 (3.2)	2 (4.0)	0.781
Poor wound healing	5 (2.4)	3 (1.9)	2 (4.0)	0.402
Operation time, min	288 ± 95	278 ± 88	326 ± 111	0.003
Hospital stays (days)	38 ± 16	38 ± 16	40 ± 14	0.359
Lost to follow up, n (%)	41 (19.8)	9 (18.0)	32 (20.4)	0.839
In-hospital mortality, n (%)	9 (4.3)	6 (3.8)	3 (6.0)	0.511
Long-term mortality after admission, n (%) *	23 (13.9)	15 (12.0)	8 (19.5)	0.227

LSIE, left-sided infective endocarditis; LVS, left-sided valve surgery only; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty.

*N = 166 excluded 41 patients lost to follow up.

N = 157 excluded 41 patients lost to follow up and 9 patients died during hospitalization.

Variables	All (n = 207)	LVS (n = 157)	LVS + TA (n = 50)	<i>P value</i>
Long-term mortality after discharge, n (%) #	14 (8.9)	9 (7.6)	5 (13.2)	0.292
LSIE, left-sided infective endocarditis; LVS, left-sided valve surgery only; LVS + TA, left-sided valve surgery with concomitant tricuspid annuloplasty.				
*N = 166 excluded 41 patients lost to follow up.				
# N = 157 excluded 41 patients lost to follow up and 9 patients died during hospitalization.				

The average length of hospitalization was 38 ± 16 days and no significant differences were indicated in hospital stays between the two groups.

Effect of concomitant TA on mortality

Of the 207 patients, there were 9 (4.3%) deaths during hospitalization. With a median follow-up duration of 34.4 (IQR 19.8–56.3) months, 14 (8.9%) patients died after discharge (**Table 3**). A total of 41 (19.8%) patients lost to follow up. However, demographic and baseline characteristic and complications data between follow-up and lost-to-follow-up were comparable (**Supplementary Table 1–2**). No significant differences were indicated in in-hospital mortality nor long-term mortality between the LVS group and the LVS + TA group. After being adjusted for Pitt bacteremia score and eGFR, concomitant TA was not significantly associated with in-hospital mortality nor long-term mortality. However, Pitt bacteremia score was significantly associated with poor short-term and long-term prognosis ($P < 0.001$) (**Table 4–5**).

Table 4
Unadjusted and adjusted multivariable analyses of risk factors associated with mortality during index admission.

Variables	Unadjusted		Adjusted	
	OR (95% CI)	<i>P value</i>	OR (95% CI)	<i>P value</i>
Pitt score	1.557 (1.253–1.934)	< 0.001	1.550 (1.232–1.951)	< 0.001
eGFR	0.988 (0.968–1.008)	0.244	0.997 (0.976–1.019)	0.800
Concomitant TA	1.606 (0.387–6.673)	0.514	1.757 (0.323–9.570)	0.515
OR, odds ratio; CI, Confidence interval; TR, tricuspid regurgitation; TA, tricuspid annuloplasty.				

Table 5

Unadjusted and adjusted multivariable analyses of risk factors associated with long-term mortality after index admission or after discharge.

Variables	Unadjusted		Adjusted	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Survival after index admission				
Pitt score	1.535 (1.317–1.790)	< 0.001	1.508 (1.281–1.75)	< 0.001
eGFR	0.983 (0.970–0.996)	0.010	0.995 (0.983–1.008)	0.474
Concomitant TA	1.682 (0.677–4.179)	0.263	1.912 (0.742–4.928)	0.209
Survival after discharge				
Pitt score	1.531 (1.229–1.907)	< 0.001	1.522 (1.202–1.928)	< 0.001
eGFR	0.982 (0.966–0.999)	0.038	0.993 (0.977–1.010)	0.435
Concomitant TA	2.300 (0.745–7.099)	0.148	2.693 (0.830–8.741)	0.099

Discussion

As a common manifestation in LSIE, functional TR is thought to be associated with progressive right-sided heart failure and poor prognosis. The principle of concomitant TA at the time of LVS with certain indications was developed by virtue of other valvular diseases, including rheumatic heart disease and degenerative valvular heart disease [13]. However, there is a paucity of available evidence to elaborate on whether concomitant TA improves the prognosis of LSIE. Our study revealed that concomitant TA had significantly advanced effects on TR severity alleviation, right atrial dimension diminution, afterload reduction, as well as right heart function enhancement. However, concomitant TA at the time of LVS was associated with prolonged operation time, increased perioperative complications without improved short-term nor long-term prognosis.

In left-sided heart diseases, the right ventricular afterload usually increases (with or without pulmonary hypertension), followed by right ventricular remodeling and tricuspid annular dilation. Tricuspid annular dilation further results in poor leaflet apposition and leaflet coaptation mode, which eventually leads to functional TR [8]. The prevalence of functional TR with or without tricuspid annular dilatation in patients undergoing surgery for mitral regurgitation has ranged from 8–65% [29–31]. Patients with higher functional TR was independently associated with worse prognosis [32]. According to previous study, concomitant TA at the time of LVS in patients with functional moderate to severe TR was associated with decreased TR degree and late TR progression, improved right ventricular function and remodeling, as well as better long-term prognosis without increasing surgical risks [33–39]. Left uncorrected at the time of LVS, mild or moderate degrees of functional TR may progress over time in approximately 25% of patients, and reoperation was associated with high mortality, resulting in reduced long-term survival [13, 40]. Therefore, concomitant TA procedure for moderate to severe TR in left-sided surgery is a class I recommendation according to the American College of Cardiology/ American Heart Association and the European Society of Cardiology [13, 41].

However, according to Society of Thoracic Surgeons Adult Cardiac Surgery Database (STSACSD, version 2.73, 2011 to 2013), only 79% of patients with severe TR and 39% of patients with moderate TR undergo concomitant TA at the time of mitral surgery, possible due to the concern of safety and increased mortality or postoperative complications [42]. In our study, moderate to severe TR was presented in up to 24.8% of LSIE patients (**Supplementary Table 3–4**). Concomitant TA was performed in 50/207 (24.2%) of patients undergoing LVS in our current study, including 22/143 (15.4%) of patients with mild TR accompanied with tricuspid annulus dilation, and 24/45 (53.3%) with moderate TR and 4/4 (100%) of patients with severe TR. The TR severity was significantly improved after LVS independent of TA and the attenuation of TR in the LVS + TA group was significantly greater than that without TA, which was consistent with previous study [36]. The RA diameter and PASP were also significantly reduced after concomitant TA.

However, in our current study, concomitant TA at the time of LVS was associated with increased procedure time and postoperative complications without improved prognosis. According to previous study, operative mortality was almost double for multiple-valve procedures as compared with single-valve procedures. Moreover, patients with emergency status and endocarditis were significant associated with increased mortality in multiple-valve procedure [42]. Nearly one-quarter of IE patients with surgical indications do not undergo surgery, and operation for active IE was associated with high risk, with an overall in-hospital mortality of 20% [43, 44]. The possible reason was that patients with LSIE are usually urgent and progressive rapidly, which are quite different from rheumatic heart disease and degenerative heart disease with relatively latent progression and long duration. Therefore, whether functional tricuspid regurgitation should be treated at the time of LVS in patients with LSIE needs further robust clinical trials and evidence.

Another interesting finding in our study was that the risk of systemic embolisms was reduced in moderate to severe TR group (**Supplementary Table 4**), which was also elucidated among mitral stenosis patients in a previous study [45]. We speculate that the underlying rationale behind is the reduction of pulmonary arterial and venous flow with subsequent resolution of congestion and stasis in the left atrium [45].

Strengths And Limitations

To our knowledge, this is the first study evaluating the prognosis of concomitant TA in LSIE patients who underwent LVS. Nevertheless, this present study has several limitations. First, our study was a single-center retrospective study with quite small sample size, with inevitable selection bias to some extent. For instance, the proportion of patients with valve replacement in our study was remarkable higher than what the guideline recommends, possibly attributable to higher referral rate of surgery-suitable patients from regional hospitals and surgeon selection bias. Second, the diameter of tricuspid annulus was not routinely measured in our center over the study period, consequently we were not able to present and investigate the relationship between tricuspid annulus dilation and prognosis. Third, the rate of loss to follow-up was quite high in our study, however, the baseline characteristics were overall comparable. Although it's not easy to carry out a randomized control trial due to the relatively low incidence rate, further robust prospective multicenter randomized control trials with long-term follow-up are still necessary to explicate the prognostic value of concomitant TA with LVS in LSIE patients.

Conclusion

Concomitant TA at the time of LVS significantly improved cardiac diameter but increased postoperative complications. It might not be associated with improved survival in LSIE patients.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest.

Authors' contributions

All the authors contributed to the design and development of the study, and reviewed the manuscript prior to submission. Yugang Dong and Chen Liu conceived and instructed the study. Zexuan Wu and Yuanyuan Zhou designed the study. Zexuan Wu wrote the original draft while Yili Chen and Fangfei Wei revised it. Zi Ye contributed to the English language editing. Xin He and Weihao Liang provided statistical expertise and supported the development of the statistical analysis plan. Jingjing Zhao, Ruicong Xue, Yuzhong Wu and Wengen Zhu supported the data collection as well as the follow up of the patients.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

This study is a retrospective observational study with data collected from the electronic medical records of The First Affiliated Hospital of Sun Yat-Sen University. Informed consent was exempted in the study.

Data Availability Statement

All data used during the study are available from the corresponding author by request.

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Figures

Figure 1

Flowchart of the study. IE, infective endocarditis; LSIE, left-sided infective endocarditis; LVS, left-sided valve surgery only; LVS+ TA, left-sided valve surgery with concomitant tricuspid annuloplasty.

Supplementary Files

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