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Cost-Effectiveness Analysis of the Triclip™ Transcatheter Tricuspid Valve Repair System in Patients with Tricuspid Regurgitation

ORIGINAL INVESTIGATION

ABSTRACT

Background: Tricuspid regurgitation is a condition that affects 1.6 million patients in the United States and is independently associated with morbidity and mortality. The TriClip™ procedure repairs the tricuspid valve without the need for open-heart surgery. The aim of this study is to evaluate the cost-effectiveness of TriClip™ treatment in patients with advanced tricuspid regurgitation from the Turkish reimbursement agency perspective.

Methods: Within the scope of this study, the general literature was searched in order to reach data on tricuspid regurgitation. The utilization of health care services used in the expert panel was re-calculated with the current reimbursement costs to determine the cost of heart failure in Turkey. In this study, Markov analysis, Tornado analysis, cost-effectiveness analysis, and partitioned survival analysis have been performed to determine whether TriClip™ is an effective treatment method compared to medication treatment.

Results: In according to calculations, 5-year survival rate was found as 49.91% for medication treatment and 57.64% for TriClip™ treatment. According to the analysis performed, the cost of medication treatment was calculated as €3879.72 and TriClip™ Transcatheter Tricuspid Valve Repair System treatment as €25 661.15 for a 60-month period in patients with tricuspid regurgitation and New York Heart Association III-IV. In the calculation, it was found that TriClip™ treatment gave patients an average of 1.64 life years and it was found to be cost-effective compared to medication treatment.

Conclusions: Considering the positive effect of TriClip™ treatment on patients with tricuspid regurgitation in terms of mortality and regression of the heart failure stage, as recommended in the guidelines, widespread of its use has great importance.

Keywords: Tricuspid valve repair, tricuspid regurgitation, transcatheter interventions, cost-effectiveness

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INTRODUCTION

Tricuspid regurgitation (TR) is a relatively common medical abnormality. Echocardiography is the best technique for diagnosis since the patients are usually asymptomatic and cannot be detected by physical examination.[1,2] Tricuspid regurgitation is a condition that affects 1.6 million patients in the United States and is independently associated with morbidity and mortality.[3] Tricuspid regurgitation starts in the ages of 40-50 in general and has the highest incidence in the ages of 70-80s.[4]

Compared to the extensive literature on the prevalence, pathophysiology, and outcome of heart diseases, data on TR are very limited.[5] However, it is estimated that its prevalence in the general population is around 1%[6] and approximately 80%-90% of cases are due to secondary causes.[7,8] Despite the limited number of studies, when the epidemiology of TR was examined, it has been concluded that it is seen at higher rates in women.[4-6] In addition, studies have proven that the prevalence and severity of TR increase as the age increases.[5]

Treatment Options for Tricuspid Regurgitation

While the treatment options for TR vary in accordance with the disease being primary or secondary and its severity, basic treatment options include

medical treatment, surgical applications, and transcatheter interventions.

Medical Treatment

There is no medical treatment that targets TR directly. Medical treatments are often applied to ease heart failure symptoms. Medications that target the renin–angiotensin system such as diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, beta-blockers, and digital group medications are listed as the most basic medications used in the treatment of heart failure due to TR.[9]

Surgical Applications

As another treatment option, valve surgery is recommended as a standard treatment for patients with symptomatic and asymptomatic secondary TR who will undergo left-sided valve surgery by the American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines due to the progressive course of right ventricular dilatation.[10,11] Surgical treatment options that can be performed are valve replacement or valve repair.[12] Although more than 1.6 million patients in the United States have moderate TR, less than 8000 tricuspid valve operations are performed annually.[9] Because significant TR appears to be a marker for late myocardial and valvular heart disease, repeated surgeries for recurrent TR are particularly high-risk surgical procedures. In-hospital mortality can be up to 37% in repeated operations in TR, and therefore, it is not recommended routinely for many patients.[13]

Transcatheter Interventions

The risks and inadequate clinical results related to isolated tricuspid surgery have led to the research and development of minimally invasive approaches for tricuspid valve repair.[14] Patients with severe TR are often considered inoperable due to comorbidities, and surgery is therefore often rejected. Hence, there is a great unfulfilled need for less invasive treatment options.[15]

In this study, transcatheter tricuspid valve repair, which was evaluated clinically and economically and is an up-to-date treatment option, was first applied in 2015.[16] TriClip leverages the same clip-based technology as MitraClip but has a differentiated delivery system designed specifically for delivery to the tricuspid valve. The TriClip™ procedure repairs the tricuspid valve without the need for open-heart surgery. This approach allows the heart to pump blood more efficiently, relieving symptoms of TR and improving a person's quality of life while this approach is still investigated.[17] The TriClip™ device is advised for patients with severe TR with valve anatomic coaptation gaps of ≤1cm, who are at high risk for tricuspid valve surgery, do not have severe mitral regurgitation or severe pulmonary hypertension, and are symptomatic despite medical therapy.[18] Risk factors in terms of open surgery include old age, disease etiology, presence of comorbid conditions, previous mitral valve intervention, severe TR, advanced heart failure, and expected surgery-specific risks.[15,19]

HIGHLIGHTS

- The TriClip™ procedure repairs the tricuspid valve without the need for open-heart surgery.
- In the comparison between medication treatment and TriClip™ treatment in the analyses, it has been found that although its upfront cost was higher, TriClip™, which was clinically more effective, was found to be more cost-effective than medication treatment.
- TriClip™ treatment gave patients an average of 1.64 life years.

The aim of this study is to evaluate the cost-effectiveness of TriClip™ transcatheter tricuspid valve repair system treatment in patients with advanced TR from the Turkish reimbursement agency perspective.

METHODS

Data Gathering

Within the scope of this study, general literature was searched in the databases of the National Thesis Center, Google Scholar, Google Books, and PubMed in order to access data on the prevalence, mortality rates, treatment rates, and costs of TR.

Clinical Data

According to the TR prevalence data based on age and gender obtained from the study conducted by Singh et al.[6] the prevalence rate of TR in the population was found to be approximately 1%. The prevalence of moderate and severe TR in men and women by age was calculated in accordance with the TR degrees by age and gender given in the study (Table 1):

$$\text{Tricuspid regurgitation}_{\text{moderate to severe}} = \left(\left(\frac{\text{Male}_{\text{moderate to severe}}}{\text{Male}_{\text{early}} + \text{Male}_{\text{mild}} + \text{Male}_{\text{moderate to severe}}} \right) + \left(\frac{\text{Female}_{\text{moderate to severe}}}{\text{Female}_{\text{early}} + \text{Female}_{\text{mild}} + \text{Female}_{\text{moderate to severe}}} \right) \right) / 2$$

$$\begin{aligned} &\text{General tricuspid regurgitation}_{\text{moderate to severe}} \\ &= \left(\text{TRMF}_{26-39\,\text{OI}} * \left(\text{M}_{26-39\,\text{HS}} + \text{F}_{26-39\,\text{HS}}\right)\right) + \left(\text{TRMF}_{40-49\,\text{OI}} * \left(\text{M}_{40-49\,\text{PN}} + \text{F}_{40-49\,\text{PN}}\right)\right) \\ &+ \left(\text{TRMF}_{50-59\,\text{MS}} * \left(\text{M}_{50-59\,\text{PN}} + \text{F}_{50-59\,\text{PN}}\right)\right) + \left(\text{TRMF}_{60-69\,\text{MS}} * \left(\text{M}_{60-69\,\text{PN}} + \text{F}_{60-69\,\text{PN}}\right)\right) \\ &+ \left(\text{TRMF}_{70-83\,\text{MS}} * \left(\text{M}_{70-83\,\text{PN}} + \text{F}_{70-83\,\text{PN}}\right)\right) / \left(\text{Male}_{26-39\,\text{PN}} + \text{Male}_{40-49\,\text{PN}}\right. \\ &+ \text{Male}_{50-59\,\text{PN}} + \text{Male}_{60-69\,\text{PN}} + \text{Male}_{70-83\,\text{PN}} \\ &+ \left(\text{Female}_{26-39\,\text{PN}} + \text{Female}_{40-49\,\text{PN}} + \text{Female}_{50-59\,\text{PN}} + \text{Female}_{60-69\,\text{PN}}\right. \\ &+ \left.\text{Female}_{70-83\,\text{PN}}\right) \end{aligned}$$

where TRMF = tricuspid regurgitation in male and female; MS = moderate to severe; M = male; F = female; PN = patient number.

It has been observed that as the age and clinical stage of the disease increased, the mortality rate also increased.

Table 1. Prevalence of Tricuspid Regurgitation and Life Expectancy Calculation

	Age, 26-39	Age, 40-49	Age, 50-59	Age, 60-69	Age, 70-83
Moderate to severe tricuspid regurgitation men and women	0.75%	0.48%	0.59%	0.95%	4.27%
Moderate to severe tricuspid regurgitation general rates	0.88%				

Source: Singh et al.[6]

The average age of individuals with moderate and severe TR was calculated as 60.7. The remaining life expectancy for males in the average age group determined by the date published by the Turkish Statistical Institute (TÜİK) is 16.88; for females, it is 19.94. Therefore, the average remaining life expectancy is taken as 18.41 which is the average of males and females[20]:

$$\text{Average life expectancy}_{61} = \left(\text{average life expectancy}_{\text{male; 61}} + \text{average life expectancy}_{\text{female; 61}}\right) / 2$$

$$\text{Life years gained}_{\text{medical treatment}} = \left(1 - \text{recovery}_{\text{medical treatment}}\right) * \text{average life expectancy}_{61}$$

$$\text{Life years gained}_{\text{TVRT}} = \left(1 - \text{recovery}_{\text{TVRT}}\right) * \text{average life expectancy}_{61}$$

$$\text{Life years gained} = \text{life years gained}_{\text{TVRT}} - \text{life years gained}_{\text{medical treatment}}$$

where TVRT = TriClip™ transcatheter tricuspid valve repair treatment.

The calculation of mortality rates was made by taking the weighted average in accordance with the literature. Monthly observed mortality rates were calculated according to New York Heart Association (NYHA) based on the calculated mortality and follow-up period averages (Table 2):

$$\begin{aligned}\text{NYHA I-II}_{\text{mortality}} = {} & \left(\text{NYHA I}_{\text{M;S1}} * \text{NYHA I}_{\text{PN;S1}} + \text{NYHA I}_{\text{M;S2}} * \text{NYHA I}_{\text{PN;S2}} \right. \\ & + \text{NYHA I}_{\text{M;S3}} * \text{NYHA I}_{\text{PN;S3}} + \text{NYHA I}_{\text{M;S4}} * \text{NYHA I}_{\text{PN;S4}} \\ & + \text{NYHA II}_{\text{M;S1}} * \text{NYHA II}_{\text{PN;S1}} + \text{NYHA II}_{\text{M;S2}} * \text{NYHA II}_{\text{PN;S2}} \\ & \left. + \text{NYHA II}_{\text{M;S3}} * \text{NYHA II}_{\text{PN;S3}} + \text{NYHA II}_{\text{M;S4}} * \text{NYHA II}_{\text{PN;S4}} \right) \\ & / \left(\text{NYHA I}_{\text{PN;S1}} + \text{NYHA I}_{\text{PN;S2}} + \text{NYHA I}_{\text{PN;S3}} + \text{NYHA I}_{\text{PN;S4}} \right. \\ & \left. + \text{NYHA II}_{\text{PN;S1}} + \text{NYHA II}_{\text{PN;S2}} + \text{NYHA II}_{\text{PN;S3}} + \text{NYHA II}_{\text{M;S4}} \right)\end{aligned}$$

$$\begin{aligned}\text{NYHA III-IV}_{\text{mortality}} = {} & \left(\text{NYHA II}_{\text{M;S3}} * \text{NYHA II}_{\text{PN;S3}} + \text{NYHA II}_{\text{M;S4}} * \text{NYHA II}_{\text{PN;S4}} \right. \\ & = \left(\text{NYHA III}_{\text{M;S1}} * \text{NYHA III}_{\text{PN;S1}} + \text{NYHA III}_{\text{M;S2}} * \text{NYHA III}_{\text{PN;S2}} \right. \\ & + \text{NYHA III}_{\text{M;S3}} * \text{NYHA III}_{\text{PN;S3}} + \text{NYHA III}_{\text{M;S4}} * \text{NYHA III}_{\text{PN;S4}} \\ & + \text{NYHA IV}_{\text{M;S1}} * \text{NYHA IV}_{\text{PN;S1}} + \text{NYHA IV}_{\text{M;S2}} * \text{NYHA IV}_{\text{PN;S2}} \\ & \left. + \text{NYHA IV}_{\text{M;S3}} * \text{NYHA IV}_{\text{PN;S3}} + \text{NYHA IV}_{\text{M;S4}} * \text{NYHA IV}_{\text{PN;S4}} \right) \\ & / \left(\text{NYHA III}_{\text{PN;S1}} + \text{NYHA III}_{\text{PN;S2}} + \text{NYHA III}_{\text{PN;S3}} + \text{NYHA III}_{\text{PN;S4}} \right. \\ & \left. + \text{NYHA IV}_{\text{PN;S1}} + \text{NYHA IV}_{\text{PN;S2}} + \text{NYHA IV}_{\text{PN;S3}} + \text{NYHA IV}_{\text{M;S4}} \right)\end{aligned}$$

where M = mortality; S study; PN = patient number.

Early and 6-month follow-up NYHA distribution rates were obtained from the patients who received TriClip™ transcatheter tricuspid valve repair system treatment from a study conducted by Nickenig et al.[14] Based on these values, the stages were calculated in accordance with the rate of regression of heart failure during the follow-up period in

Table 2. NYHA Mortality Rates Based on Stages

		NYHA Stages				Mortality, %			
Total Number of Patients	**Follow-Up Period (Month)**	**I**	**II**	**III**	**IV**	**I**	**II**	**III**	**IV**
988[1]	38.5	196	574	206	12	14.3	21.3	35.9	58.3
3276[2]	37.0	1863		1863		34.4		41.7	
23[3]	60.0	0	18	4	1		11.1	50.0	
293[4]	6.0	97		99	97	19.6		34.3	39.2

[1]Ahmed et al.[21]
[2]Ahmed et al.[22]
[3]Karavelioğlu et al.[23]
[4]Holland et al.[24]
NYHA, New York Heart Association.

patients who received TriClip™ transcatheter tricuspid valve repair system treatment.

$$\text{NYHA III-IV}(\%)_{6-\text{month change}} = \frac{\left(\text{NYHA III-IV}(\%)_{\text{early}} - \text{NYHA III-IV}(\%)_{\text{month 6}}\right) - 1}{6}$$

Economic Data

Rates and costs of patients to calculate the cost of TR were obtained from literature data. Follow-up cost of heart failure in Turkey was calculated by an expert panel with broad participation in 2015 within the scope of the Project of Determination of Disease Management and Cost Components for Heart Failure in Turkey. The utilization of health care services used in the expert panel was re-calculated with the current reimbursement costs to determine the cost of heart failure in Turkey. Consulting to emergency service, cost of intensive care stay, medical visit fees, consultation and laboratory costs, and non-medication treatment costs have been obtained from Health Practices Statement (SUT) Annex 2A Outpatient Payment List, Annex 2B Transaction Point per Service List, Annex 2C Transaction Point based on Diagnosis List, Annex 3H Cardiology, Annex 3I Cardiovascular Surgery List, and medication costs from Turkish Medicines and Medical Devices Agency (TİTCK) Detailed Medication Price List, and SUT Annex 4A Payable Medication List regarding the current cost of the disease. Analyses have been made with direct cost considering the public reimbursement perspective. The exchange rates as 1 Euro = 7,9717 Turkish Liras for 2020 were used for conversation.

Medical visits used in the analysis include cardiology, internal diseases, cardiovascular surgery, and other medical visits; examinations include chest x-ray, electrocardiography, echocardiogram, exercise test, Holter monitorization, myocardial perfusion scintigraphy, renal function tests (BUN (Blood Urea Nitrogen), creatinine) + blood sugar, estimated glomerular filtration rate, liver function tests (ALT (alanine aminotransferase), AST (Aspartat Aminotransferaz), AP (alkaline phosphatase), LDH (lactate dehydrogenase), bilirubin, GGT (gamma-glutamyl transferase)), electrolytes (Na, K, Cl, Ca, P) lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride), NT-proBNP (N-terminal proB-type Natriuretic Peptide) and BNP (B-type Natriuretic Peptide), CK (creatine kinase) and troponin, microalbuminuria, thyroid function tests (free T3 (Triiodothyronine), free T4 (Thyroxine), TSH (Thyroid-stimulating hormone), thyroglobulin), complete blood count, coagulation tests (PT (Prothrombin Time), aPTT (activated partial thromboplastin time), INR (International normalised ratio)), and blood gas tests; medications include furosemide PO, beta-blockers, ACE (angiotensin converting enzyme) inhibitors, ARB (angiotensin-receptor blockers), spironolactone, digoxin PO (per os (by mouth)), ivabradine, oral nitrate, ASA (acetylsalicylic acid), warfarin, nitroglycerin, intravenous digoxin, dobutamine, dopamine, devosimendan, and heparin; non-medication treatments include implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy pacemaker (CRT-P), cardiac resynchronization therapy defibrillator (CRT-D), Left Ventricular Assist Devices (LVAD), heart transplantation, and physical therapy:

$$\begin{aligned}
&\text{Cost of heart failure}_{\text{Turkey}} \\
&= \text{outpatient follow-up cost} + \text{emergency service cost} \\
&+ \text{intensive care stay cost} + \text{normal service stay cost} \\
&+ \text{medication cost} + \text{non-medication cost}
\end{aligned}$$

$$\begin{aligned}
&\text{Outpatient follow-up cost}_{\text{Turkey}} \\
&= \left(\text{doctor's appointment}_{\text{unit cost}} * \text{average visit number}\right) \\
&+ \left(\text{consultation}_{\text{unit cost}} * \text{average consultation number}\right) \\
&+ \left(\text{examination}_{\text{average cost}} * \text{average test number}\right)
\end{aligned}$$

$$\begin{aligned}
&\text{Emergency service cost}_{\text{Turkey}} \\
&= \left(\text{emergency service application}_{\text{unit cost}} * \text{average} \right. \\
&\left. \text{emergency service application}\right) \\
&+ \left(\text{consultation}_{\text{unit cost}} * \text{average consultation number}\right) \\
&+ \left(\text{examination}_{\text{average cost}} * \text{average test number}\right)
\end{aligned}$$

$$\begin{aligned}
&\text{Intensive care stay cost}_{\text{Turkey}} \\
&= \left(\text{intensive care stay}_{\text{unit cost}} * \text{average intensive care stay day}\right) \\
&+ \left(\text{consultation}_{\text{unit cost}} * \text{average consultation number}\right) \\
&+ \left(\text{examination}_{\text{average cost}} * \text{average test number}\right)
\end{aligned}$$

$$\begin{aligned}
&\text{Normal service stay cost}_{\text{Turkey}} \\
&= \left(\left(\text{normal service stay}_{\text{unit cost}} * \text{average normal service stay day}\right)\right. \\
&+ \left(\text{transfer from ICU to normal service}_{\text{unit cost}}\right. \\
&\left.\left. * \text{averagenormal service stay day after intensive care}\right)\right) \\
&+ \left(\text{consultation}_{\text{unit cost}} * \text{average consultation number}\right) \\
&+ \left(\text{examination}_{\text{average cost}} * \text{average test number}\right)
\end{aligned}$$

$$\begin{aligned}
&\text{Medication cost}_{\text{Turkey}} \\
&= \left(\text{medications used in outgoing monitoring}_{\text{unit cost(try/day)}}\right. \\
&\left. * \text{average medication numbers used in outgoing monitoring}_{\text{day/year}}\right) \\
&+ \left(\text{medications used in hospital stay}_{\text{unit cost(try/day)}}\right. \\
&\left. * \text{average medication number used in hospital stay}_{\text{day/year}}\right)
\end{aligned}$$

$$\text{Non-medication treatment cost}_{\text{Turkey}} = \left(\text{non-medication treatment}_{\text{unit cost}} * \text{average non-medication treatment usage}\right)$$

Data related to average treatment cost in accordance with NYHA classification in patients with heart failure were taken from the studies conducted by Delgado et al[25] and Czech et al[26] The exchange rate of cost between stages in accordance with NYHA classification was calculated in patients with heart failure in accordance with these studies.

New York Heart Association average cost and stage costs for each study have been calculated separately using the following formula:

$$\text{NYHA}(\%)_{\text{average cost vs. stage cost}} = \frac{\text{NYHA}_{\text{average cost}} - \text{NYHA}_{\text{stage cost}}}{\text{NYHA}_{\text{average cost}}}$$

After calculating the average NYHA cost and the stage cost difference for each study, the stage cost difference of the studies compared to the average has been calculated by the following formula:

$$\text{NYHA}(\%)_{\text{average cost versus stage cost}} = \frac{\text{NYHA}_{\text{SC;S1}} + \text{NYHA}_{\text{SC;S2}} + \text{NYHA}_{\text{SC;S3}}}{3}$$

where SC = stage cost and S = study.

*The costs between stages in Turkey have been calculated by dividing the exchange rates calculated to the costs of heart failure in Turkey:

$$\text{Heart failure cost}_{\text{NYHA stage}} = \text{heart failure cost}_{\text{Turkey}} * \left(1 + \text{NYHA average and stage difference}(\%)_{\text{Stage}}\right)$$

This calculation has been made at each stage.

TriClip™ transcatheter tricuspid valve repair system treatment has been calculated based on the current exchange rate of Euro and has been included in the calculation as 23 000 Euro. No discount ratio has been used in the model.

Model Analysis

Although the effects of transcatheter valve repair treatment on heart failure are known, there is no literature information on the effect on mortality since long-term studies have not been concluded. Therefore, the Markov model has been adopted to reduce mortality to be obtained by TriClip™ transcatheter tricuspid valve repair System. Markov models represent a patient's state as a collection of mutually exclusive and exhaustive health states, with the patient is in one and only one of them at a time. Transitions from one state to another represent all possible outcomes. Every state has a cost and an effectiveness value associated with it. The net benefit of each intervention is determined by the total cost and effectiveness over time.[27] The TreeAge Healthcare Pro 2020 program has been used in the setup and analysis of the Markov model.

In the designed model (Figure 1), the change between stages determined by NYHA stated in the study conducted by Nickenig et al[14] and mortality rates and medical treatment cost change in accordance with the NYHA stages taken from the literature have been used in the Markov model. Since there is no long-term information on mortality reduction with TriClip™ transcatheter tricuspid valve repair system, it has been acknowledged that the improvement in NYHA stages obtained from the literature may hypothetically provide a reduction in mortality compared to expected mortality rates in NYHA stages. The costs of heart failure in accordance with NYHA stage demonstrated in studies conducted by Delgado et al[25] and Czech[26] have been included in the model by applying them to the costs of heart failure in Turkey. In the Markov model, the time horizon has been taken as 60 months.

Sensitivity Analysis

Sensitivity analysis is performed to examine how the uncertainty in the output of a model (numerical or otherwise) can be distributed to different sources of uncertainty in the model input,[28] in other words, to evaluate the effect of the factors in the model on the results of the study.[29] Tornado analysis has been adopted as sensitivity analysis in the designed Markov model.

In economic evaluations, Tornado diagrams are used to present the result of multiple univariate sensitivity analysis on a single graph. Tornado diagrams allow the researcher to evaluate which parameters of the model have the greatest impact on the results. Typically, as the horizontal lines, those with the largest span (parameters to which the model output is most sensitive) are lined up at the top of the diagram, while those with the lowest span are at the bottom.[30] The Tornado diagram summarizes the impact of each variable on the merit figure. Thus, the diagram has the typical funnel shape of a tornado. Tornado diagrams also play an important role in the decision-making process in terms of identifying critical variables in the results.[31] In the Tornado analysis, the comparison has been made in accordance with the calculation of different scenarios based on each 1% exchange in the range of ±15% of the factors used in the model. The Tornado analysis has been performed with TreeAge Healthcare Pro 2020 program.

Partitioned Survival Analysis

In this study, partitioned survival analysis has been performed to determine the 5-year survival of patients who received TriClip™ transcatheter tricuspid valve repair system treatment and medication treatment that are among the treatment alternatives for TR. The partitioned survival analysis is a type of economic model used to monitor a theoretical cohort over time as it moves between a range of comprehensive and mutually exclusive health conditions. The model estimates the rate of a cohort in each case based on parametric survival equations. Such models are often used to model cancer treatments with separate survival equations for general survival and progression-free survival.[32] The partitioned survival analysis simulates the probability that a patient will be in each of the different health conditions at a

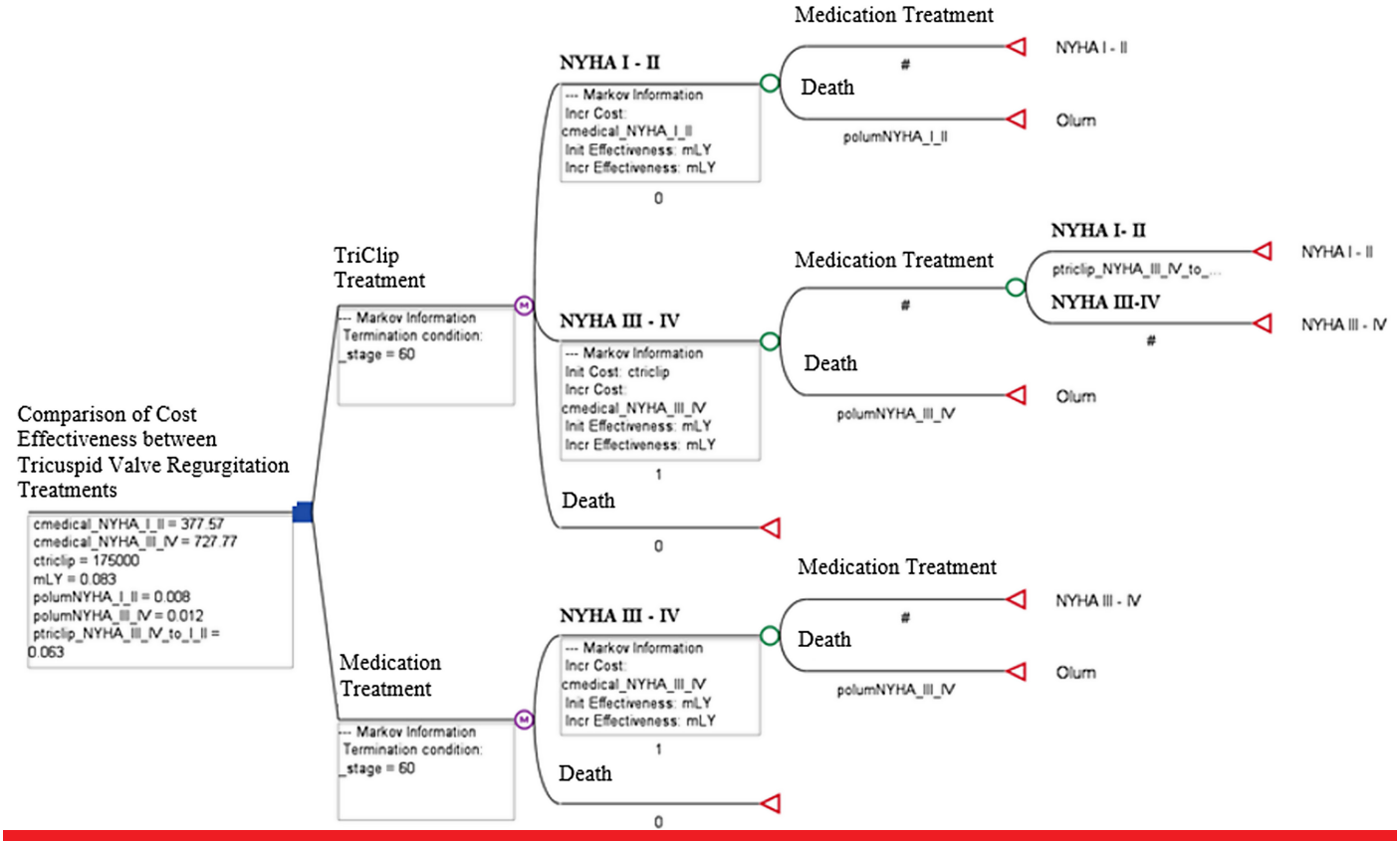


Figure 1. Markov Model Scheme.

given time point when treated with a particular treatment.[33] Partitioned survival models are routinely used to inform reimbursement decisions for oncology drugs by National Institute for Health and Care Excellence (NICE).[34] The partitioned survival analysis has been conducted with TreeAge Healthcare Pro 2020.

Incremental Cost-Effectiveness Ratio

In this study, the incremental cost-effectiveness ratio (ICER) has been performed to determine whether TriClip™ transcatheter tricuspid valve repair system is an effective treatment method compared to medication treatment. Incremental cost-effectiveness ratio is identified as the ratio of the cost difference between the 2 interventions to the difference in effectiveness. It is calculated as a measure of additional cost per health gain. Incremental cost-effectiveness ratio allows to evaluate the balance between patient results obtained and resources spent.[35] In order to make an objective judgment on the value revealed by the ICER calculation, a threshold value determination approach has been developed based on gross domestic product (GDP) per capita by the World Health Organization. According to the calculation of the World Health Organization, the ICER must be 3 times less than GDP per capita in order for a treatment to be considered cost-effective. If the ICER is less than GDP per capita, it means that the cost-effectiveness of the intervention is very high. If it is between 1 and 3 times, it means that the intervention is cost-effective. And, it is considered as not cost-effective if it is more than 3 times[36]:

$$ICER^{*} = \frac{\text{Cost of TriClip}^{TM}\text{ transcatheter tricuspid valve repair system} - \text{cost of medication treatment}}{\text{Effectiveness of TriClip}^{TM}\text{ transcatheter tricuspid valve repair system} - \text{effectiveness of medication treatment}}$$

Source: Koçkaya and Wertheimer.[37]

Patient Population

Surgical treatment, medical treatment, and transcatheter valve repair treatment are considered as alternative treatment options for TR. Which treatment is an alternative to choose depends on the patient. In accordance with the information obtained through literature review, surgical treatment options pose a high risk for patients who are elderly, who underwent previous cardiac surgery, with significant cardiac and non-cardiac comorbidities (atrial fibrillation, chronic obstructive pulmonary disease, renal disease), with advanced disease sequelae (ascites, peripheral edema, etc.), with stages III and IV heart failure in accordance with NYHA classification, who are diuretic dependent, who have been hospitalized multiple times for right ventricular failure, and who have high-impact regurgitant orifice space.[38,39] Transcatheter valve repair treatment is recommended especially for patients who cannot receive such surgical treatment, asymptomatic patients with severe TR, and patients with mild or moderate TR with annular enlargement but

without the indication of cardiac surgery.[38] In this context, patients with tricuspid valve regurgitation who have developed NYHA stages III and IV heart failure are included in the model designed for transcatheter tricuspid valve treatment.

Comparison

In view of the information obtained from the literature review, there are no other treatment alternatives, including surgery, for patients with TR and advanced heart failure. However, these patients receive medical treatment for heart failure in order to take heart failure symptoms under control, even if there is no therapeutic alternative. In this context, the economic and clinic results of TriClip™ transcatheter tricuspid valve repair system treatment and medical treatment have been compared in this model.

RESULTS

Clinical Change Inputs

In the view of formulas stated in the methodology and data obtained from literature, the mortality rate calculated with the mean-weighted average for 35.5 months, which was found as the average follow-up period in the treatment of heart failure, was 0.8% per month for NYHA stages I-II and 1% per month for NYHA stages III-IV, while the average mortality rate was found to be 29.6% for NYHA stages I-II and 40.8% for NYHA stages III-IV.

According to the data obtained from published studies, the rate of recovery from stages III-IV to stages I-II was calculated monthly in accordance with the NYHA classification of patients after TriClip™ transcatheter tricuspid valve repair system treatment and the formulas stated in the methodology (Table 3).

Table 3. Reduction Rate of NYHA Stages and Rate of Change in Mortality with the Implementation of TriClip™ Transcatheter Tricuspid Valve Repair System

	Early (%)	Month 1 (%)	Month 6 (%)
NYHA I		23.0	36.0
NYHA II	25.0	57.0	51.0
NYHA III	70.0	20.0	12.0
NYHA IV	5.0		1.0
NYHA III-IV	75.0	13.0	–82.7
Monthly mortality rate change	–6.3		

NYHA, New York Heart Association.

Cost Change Inputs

The data of the Project of Determination of Disease Management and Cost Components for Heart Failure in Turkey (2015), presented in Table 4, were prepared by updating in accordance with the SUT prices in 2020.

The treatment cost of heart failure was obtained based on the stages in accordance with the published studies. Percentage cost differences of NYHA stages with respect to the average were calculated by taking the average cost of

Table 4. Annual Follow-up and Treatment Cost for Heart Failure

	Heart Failure Cost		
	2015	**2020**	**2020**
Sum total	**5128.04 TL/year**	**6017.43 TL/year**	**€754.85/year**
Outpatient follow-up	**216.54 TL/year**	**381.38 TL/year**	**€47.84/year**
Medical visit	176.31	189.88	23.82
Consultation	5.09	5.10	0.64
Examinations	35.14	186.40	23.38
Emergency service	**93.30 TL/year**	**68.62 TL/year**	**€8.61/year**
Emergency service application	10.32	9.85	1.24
Consultation	7.63	6.08	0.76
Examinations	75.35	52.69	6.61
Hospitalization at cardiology intensive care unit	**111.19 TL/year**	**125.84 TL/year**	**€15.79/year**
Hospitalization	98.74	117.25	14.71
Consultation	0.65	0.71	0.09
Examinations	11.80	7.88	0.99
Hospitalization at normal service	**206.52 TL/year**	**201.94 TL/year**	**€25.33/year**
Hospitalization	94.95	105.41	13.22
Consultation	2.05	2.25	0.28
Examinations	109.52	94.28	11.83
Medications	**715.36 TL/year**	**1111.28 TL/year**	**€139.40/year**
Outpatient monitoring	452.51	622.85	78.13
Hospitalization	262.85	488.42	61.27
Non-medication treatments	**3785.13 TL/year**	**4128.37 TL/year**	**€517.88/year**

Table 5. Cost Differences of NYHA Stages According to the Average (%)

	Average Versus II	Average Versus III	Average Versus IV
Delgado, 2014 (Direct Costs)	–22.0%	40.6%	
Czech, 2013	–31.3%	4.9%	63.6%
Delgado, 2014 (Overall Costs)	–20.7%	34.5%	
Difference according to General Average	–24.7%	26.6%	63.6%

NYHA, New York Heart Association.

the treatment specified in the studies and the difference of the stage calculated in accordance with the formulas stated in the methodology and dividing it by the average cost. The general average was calculated by taking the average of the calculated values (Table 5).

The cost of each stage of the heart failure determined by NYHA was calculated by multiplying the overall cost of heart failure treatment and the percentage difference of stage cost relative to the average in accordance with the formulas stated in the methodology. Then, NYHA stages were divided into 2 groups as I-II and III-IV. The cost of each group was calculated annually and monthly by taking the average of the costs of the stages in the group (Table 6).

Survival Results

According to calculations made with partitioned survival analysis, a 5-year survival rate was found as 49.91% for medication treatment and 57.64% for TriClip™ transcatheter tricuspid valve repair system treatment (Figure 2).

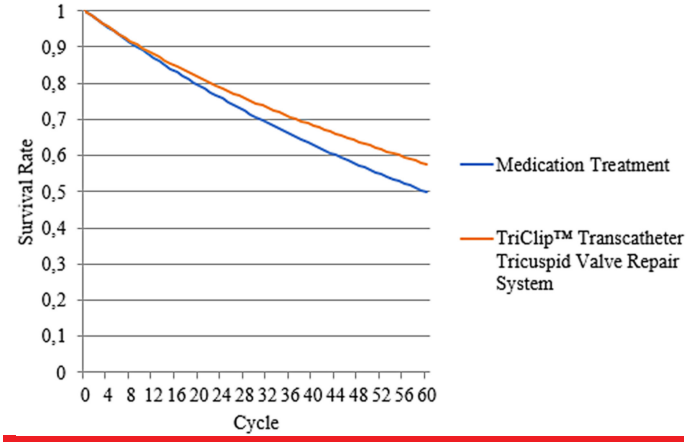


Figure 2. 5-Year Survival Rates for Medication Treatment and TriClip™ Transcatheter Tricuspid Valve Repair System Treatment Calculated with Partitioned Survival Analysis in Patients with Tricuspid Regurgitation and NYHA III-IV.

Cost-Effectiveness Outputs

According to the analysis performed, the cost of medication treatment was calculated as €3879.72 and TriClip™ transcatheter tricuspid valve repair system treatment as €25 661.15 for a 60-month period in patients with TR and NYHA III-IV. In the calculation based on the average 5-year survival rates and expected life years for TriClip™ transcatheter tricuspid valve repair system treatment and medication treatment determined by partitioned survival analysis; it was determined that TriClip™ transcatheter tricuspid valve repair system treatment gave patients an average of 1.64 life years (Table 7, Figure 3).

According to the data obtained as a result of the calculations, in the incremental cost-effectiveness ratio performed to determine whether TriClip™ transcatheter tricuspid valve repair system is a cost-effective treatment, the ICER value was calculated in accordance with the cost difference and the gained life years was found to be €13 320.41. The gross domestic product per capita in Turkey was €8152 in 2019, and 3 times of GDP per capita in Turkey has been calculated as €24 456. Since the calculated ICER value of €13 320.41 is below €24 456 which is 3 times of GDP per capita, TriClip™ transcatheter tricuspid valve repair system was found to be cost-effective compared to medication treatment in patients with TR and advanced heart failure who cannot receive another alternative treatment.

Table 6. Annual and Monthly Cost of Heart Failure in Turkey According to NYHA Stages

	Annual Average Cost	Monthly Average Cost
NYHA I- II	€568.38	€47.36
NYHA III- IV	€1,095.54	€91.30

NYHA, New York Heart Association.

In accordance with the Tornado analysis performed to determine the factors affecting the clinic effectiveness calculations, the most affecting factor in clinical effectiveness calculations is the mortality rate observed in individuals with stages III-IV advanced heart failure according to NYHA classification. It was followed by the mortality rate observed in individuals with stages I-II heart failure according to NYHA classification, and the regression of patients from stages III-IV advanced heart failure to stages I-II heart failure according to NYHA classification after TriClip™ transcatheter tricuspid valve repair system treatment (Graphic 1).

In the Tornado analysis performed to determine the factors affecting the cost results, the most affecting factor was found to be the medical treatment cost of individuals with stages III-IV advanced heart failure according to NYHA classification. It was followed by the mortality rate observed in individuals with stages III-IV advanced heart failure according to NYHA classification and the regression of the heart failure stage from stages III-IV to stages I-II in patients with advanced heart failure according to NYHA classification after TriClip™ transcatheter tricuspid valve repair system treatment. In terms of factors affecting the calculation of cost results, TriClip™ transcatheter tricuspid valve repair system treatment cost was ranked as the fourth (Graphic 2).

Table 7. Cost and Gained Life Years for Medication Treatment and TriClip™ Transcatheter Tricuspid Valve Repair System Treatment

	Cost	Survival	Expected Life Years	Cost Difference	Exp. LY. Diff.
Medication Treatment	€3879.72	0.50	10.56		
TriClip™ Transcatheter Tricuspid Valve Repair System	€25 661.15	0.58	12.19	€21 781.43	1.64

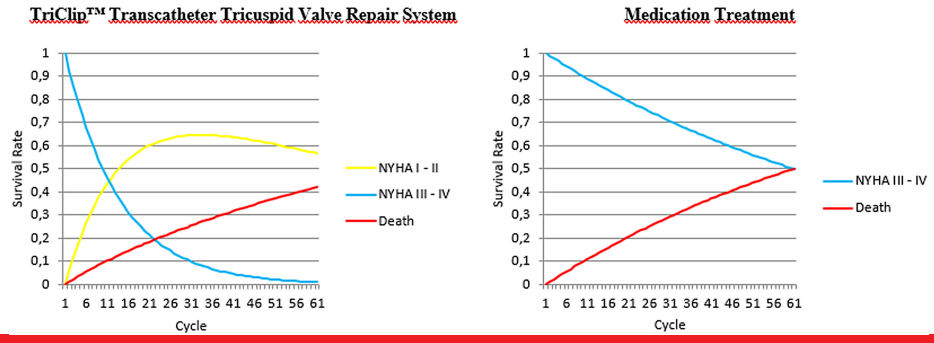
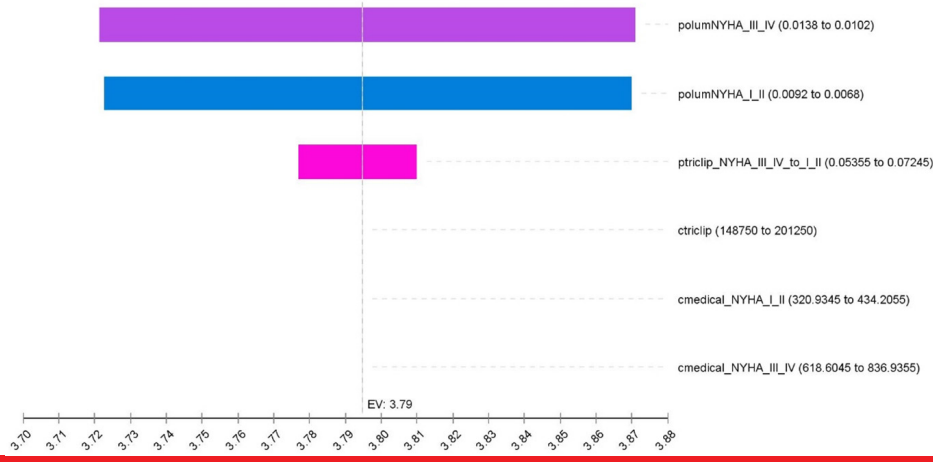


Figure 3. Distribution of Patient and Death Markov Analysis According to Medication Treatment, TriClip™ Transcatheter Tricuspid Valve Repair System, NYHA Stages.

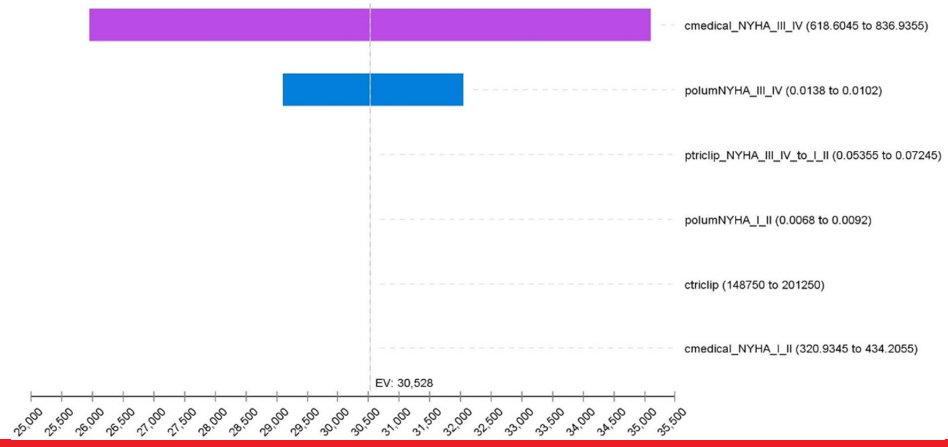


Graphic 1. Tornado Analysis – Factors Affecting Clinic Effectiveness Results.
PolumNYHA_III-IV: mortality rate observed in individuals with stages III-IV advanced heart failure;polumNYHA_I-II: mortality rate observed in individuals with stages I-II advanced heart failure;ptriclip_NYHA_III-IV_to_I-II: regression of patients from stages III-IV advanced heart failure to stages I-II heart failure after TriClip™ Transcatheter Tricuspid Valve Repair System; ctriclip: cost of TriClip™ Transcatheter Tricuspid Valve Repair System;cmedical_NYHA_I-II: cost of medical treatment in patients with stages I-II advanced heart failure;cmedical_NYHA_III-IV: cost of medical treatment in patients with stages III-IV advanced heart failure.

DISCUSSION

In this study, it was evaluated whether TriClip™ transcatheter tricuspid valve repair system is a cost-effective treatment compared to medication treatment. As a result of this study, although TriClip™ transcatheter tricuspid valve repair system treatment was more costly, it was found to be a cost-effective treatment when evaluated according to its clinical benefit. Surgical treatment has not been evaluated as it is a risky method in patients with moderate and severe TR. The clinical results of this study are consistent with the literature. However, no cost-effectiveness study on TriClip™ transcatheter tricuspid valve repair system treatment has been found in the literature.

Lurz et al[40] aimed to examine TriClip™ transcatheter tricuspid valve repair system treatment in terms of clinical benefit and safety. In this context, 85 participants were treated with TriClip™ transcatheter tricuspid valve repair system and followed for 1 year. Some of the participants could not be evaluated due to lack of follow-up and the clinical results of 63 participants were evaluated. At the end of the follow-up period, 56% (22 of 39) of patients with baseline massive or torrential TR achieved moderate or less TR at 1 year, with 90% (35 of 39) achieving at least a 1-grade reduction in TR. TR severity was significantly reduced showing a sustained TR reduction of ≥1 grade in 87% of subjects, with 70% achieving moderate or less TR at the end of the first year. In addition, the initial TR reduction (seen at 30 days) proved durable in a majority of patients (79%) at 1-year follow-up. The proportion of subjects classified as NYHA functional class I/II increased from 31% at baseline to 83% at 1 year ($P < .0001$).



Graphic 2. Tornado Analysis – Factors Affecting Clinic Effectiveness Results.
PolumNYHA_III-IV: mortality rate observed in individuals with stages III-IV advanced heart failure; polumNYHA_I-II: mortality rate observed in individuals with stages I-II advanced heart failure; ptriclip_NYHA_III-IV_to_I-II: regression of patients from stages III-IV advanced heart failure to stages I-II heart failure after TriClip™ Transcatheter Tricuspid Valve Repair System; ctriclip: cost of TriClip™ Transcatheter Tricuspid Valve Repair System; cmedical_NYHA_I-II: cost of medical treatment in patients with stages I-II advanced heart failure; cmedical_NYHA_III-IV: cost of medical treatment in patients with stages III-IV advanced heart failure.

Nickenig et al[41] evaluated the effectiveness and safety of TriClip™ transcatheter tricuspid valve repair system treatment in patients with TR. As a result of the study, it was observed that among 83 patients treated with TriClip™ transcatheter tricuspid valve repair system, 71 (86%) reduced TR by at least 1 stage within the first 30 days. In the study, which resulted in a much higher success than the targeted performance for the first 30 days, 76% success was achieved according to the 97.5% confidence limit ($P < .0001$). During the 6-month follow-up period, major adverse events were observed in 6 (5%) of 84 patients, and deaths due to all causes were reported in 4 (5%) of them. Cardiovascular mortality was reported in 3 participants, and no adverse events associated with the device were reported.

Asmarats et al[42] followed the clinical results of patients treated with the transcatheter tricuspid valve repair system for at least 24 months. Totally 19 patients with functional TR were included in the study, and the success of the procedure was achieved in 17 (89%) of them. While no mortality was reported within 30 days, deaths were reported in 4 patients (3 from terminal heart failure and 1 from sepsis) during 24-36 months follow-up. In addition, 3 (18%) patients had to be re-hospitalized due to heart failure. Of the 15 successfully treated patients with at least 2-year follow-up, improvement in NYHA functional class by ≥I grade was achieved in 14 (93%) patients, with the reduction in NYHA functional class ≥III from 93% to 34% ($P < .001$).

Study limitations

In this study, calculations were made with the Markov model since there is no mortality data related to TriClip™ transcatheter tricuspid valve repair system treatment for TR in the literature. Calculation of mortality data with the Markov model is a limitation of the study. In the event that real-life data on mortality outcomes in TriClip™ transcatheter tricuspid valve repair system treatment are obtained, the study should be re-analyzed.

Moreover, it is a limitation regarding timeliness that the data on the study taken into consideration when calculating the cost of the treatment of heart failure in Turkey were obtained from real life and expert opinion of 2015. The cost of treatment of heart failure in Turkey should be re-calculated with real-life data and up-to-date expert opinions.

CONCLUSION

In the analyses conducted, the surgical option for TR was excluded from the comparison since it carries a high risk and is not suitable for most patients. In the analyses based on the data taken from the studies in the literature, it was observed that mortality rates and costs increased as the heart failure stages progressed according to the NYHA classification. TriClip™ transcatheter tricuspid valve repair system has indirectly positive results in terms of mortality and cost since it regresses the heart failure stage compared to medication treatment.

In the comparison between medication treatment and TriClip™ transcatheter tricuspid valve repair system treatment in the analyses, it has been found that although its upfront cost was higher, TriClip™ transcatheter tricuspid valve repair system, which was clinically more effective, was found to be more cost-effective than medication treatment. Considering the positive effect of TriClip™ transcatheter tricuspid valve repair system treatment on patients with TR in terms of mortality and regression of the heart failure stage, as recommended in the guidelines, widespread of its use has great importance.

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