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Review / Derleme

Management options of valvular heart diseases after heart transplantation: A scoping review

Kalp nakli sonrası kalp kapak hastalıklarının yönetiminde seçenekler: Kapsamlı bir derleme

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ABSTRACT

Background: This study aimed to outline the valvular changes following heart transplantation and describe the management options to address these conditions.

Methods: A literature search using EMBASE, MEDLINE, and PubMed databases was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in this study. Clinical studies involving patients who had their first heart transplant and articles that mentioned management for valvular heart disease were included. Treatment options were grouped into four categories: cardiac surgery other than retransplant and valve surgery, valve replacement and repairs, nonsurgical interventions, and conservative management.

Results: Nine hundred and three (6.56%) patients out of 13,757 patients (10,529 males, 3,228 females; mean age: 60.3±10.4 years; range, 20 to 83 years) undergoing heart transplantation were identified with valvular disease affecting one or more valves. The mean interval between the transplant and the diagnosis of valve disease was 11.31±6.95 years. The most common valvular heart disease was tricuspid regurgitation, with 796 (94.09%) occurrences, followed by mitral regurgitation (n=22, 2.6%), aortic regurgitation (n=14, 1.65%), aortic stenosis (n=11, 1.3%), and mitral stenosis (n=3, 0.35%). Additionally, the number of surgical valve replacement and repairs (n=89) was higher than nonsurgical interventions (n=20).

Conclusion: Acquired valvular heart diseases after cardiac transplantation are an infrequent clinical presentation that can cause valvular changes in the recipient. According to the extracted data, there is no sole superior management option, and more research is needed in this area.

Keywords: Acquired valvular heart disease, heart transplantation, postoperative complications, transplant recipients.

ÖZ

Amaç: Bu çalışmada kalp nakli sonrası kapakçık değişikliklerinin ana hatlarıyla ortaya konulması ve bu durumlara yönelik yönetim seçeneklerinin tanıtılması amaçlandı.

Çalışma planı: Bu çalışmada, PRISMA (Sistematik Derleme ve Meta-Analizler için Tercih Edilen Raporlama Öğeleri) yönergelerine uygun olarak EMBASE, MEDLINE ve PubMed veritabanlarını içeren bir literatür taraması yapıldı. İlk kalp nakli yapılan hastaları içeren klinik çalışmalar ve kalp kapak hastalığı yönetiminden bahseden makaleler dahil edildi. Tedavi seçenekleri dört kategoride gruplandırıldı: tekrarlayan nakil ve kapak cerrahisi dışında kalp cerrahisi, kapak replasmanı ve onarımları, cerrahi olmayan müdahaleler ve konservatif yönetim.

Bulgular: Kalp nakli yapılan 13,757 hastadan (10,529 erkek, 3,228 kadın; ort. yaş: 60.3±10.4 yıl; dağılım, 20-83 yıl) 903'ünde (%6.56) bir veya daha fazla kapağı etkileyen kapak hastalığı belirlendi. Nakil ile kapak hastalığı tanısı arasındaki ortalama süre 11.31±6.95 yıl idi. En sık görülen kalp kapak hastalığı 796 (%94.09) ile triküspit yetersizliği idi ve bunu mitral yetersizlik (n=22, %2.6), aort yetersizliği (n=14, %1.65), aort darlığı (n=11, %1.3) ve mitral darlık (n=3, %0.35) takip etti. Ek olarak cerrahi kapak replasmanı ve onarımlarının sayısı (n=89), cerrahi olmayan müdahalelerden (n=20) daha yüksekti.

Sonuç: Kalp nakli sonrası edinilmiş kalp kapak hastalıkları, alıcıda kapak değişikliklerine neden olabilen nadir bir klinik tablodur. Elde edilen verilere göre, tek bir üstün yönetim seçeneği yoktur ve bu alanda daha fazla araştırmaya ihtiyaç vardır.

Anahtar sözcükler: Edinilmiş kalp kapak hastalığı, kalp nakli, ameliyat sonrası komplikasyonlar, nakil alıcıları.

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Heart transplantation remains the gold standard treatment for end-stage cardiac failure.[1] Recent developments, spanning from new mechanical circulatory support devices to the first porcine-to-human heart transplantation, show that the field of heart transplantation is evolving rapidly using novel technologies and techniques.[2] These improvements have led to improved survival after cardiac transplants, despite higher risk and more complex patients.[3] The rates of long-term survival differ among populations. Suarez-Pierre et al.[4] found that the 10-year survival in the USA was 53%, whereas it was 61% in the Scandinavian cohort conducted by Dellgren et al.[5] However, improved survival also means an increase in the incidence of long-term complications, such as cardiac allograft vasculopathy (CAV), malignancy, or valvular disease.[6]

Valvular dysfunction can cause heart failure, and in cases refractory to medical treatment, cardiac transplantation is applied as the treatment of choice.[7,8] Valvular cardiomyopathy only makes up 3% of the indications for cardiac transplantation compared to major indications such as nonischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%).[8] Although cardiac transplantation is expected to treat the underlying valve dysfunction, the changes in the valves following the transplantation may lead to a clinical presentation similar to the pretransplantation period.

A well-documented valve dysfunction following cardiac transplantation is tricuspid regurgitation (TR), the incidence of which varies from 19 to 84% based on its severity.[9] Studies on the pathophysiology of posttransplant TR show that geometric distortion of the tricuspid annulus due to central regurgitant jet and repeated endomyocardial biopsies can result in valvular dysfunction.[9-11] The former cause likely leads to functional TR, which is characterized by central regurgitant jet flow, whereas the latter causes anatomic TR due to scarring and disruption of tricuspid annulus and chordae tendineae anatomical positioning.[9]

Although there are various studies reporting the occurrence of TR after heart transplantation, as mentioned above, there is a lack of systematic evidence about other valvular diseases in this setting.[12,13] Therefore, this scoping review examines valve dysfunction following heart transplantation and delineates the management options in this setting.

MATERIALS AND METHODS

Data sources and search strategies

This scoping review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols Extension) for Scoping Reviews.[14] The literature search was performed with search terms related to valve disease and heart transplantation in the postoperative period: "cardiac transplant," "heart transplant," "valvular heart disease," "heart valve disease," "aortic valve," "pulmonary valve," "mitral valve," "tricuspid valve," "transplant recipients," and "postoperative period" in meaningful combinations with the use of Boolean operators. The following databases were searched: MEDLINE, PubMed, and EMBASE. The PROSPERO (International Prospective Register of Systematic Reviews) was also checked for any previously published reviews on the same topic. References were cross-checked to ensure a comprehensive literature search, and grey literature was adequately screened.

Eligibility criteria

The search was limited to articles written in the English language published between January 1, 2007, and April 30, 2022. In addition, only clinical studies on patients who had their first heart transplant when they were over the age of 18 and articles that mentioned the management of valvular heart disease after a heart transplant were included. Articles including patients having any kind of intervention before or during heart transplantation and patients under 18 years of age who had received a heart transplant were removed as part of the exclusion criteria.

Data characterisation, summary, and synthesis

Information about the study type, patient characteristics, diagnosis, management, and outcomes were recorded. In each study, the number of transplant patients was noted, as well as the number diagnosed with one or more types of valvular heart disease. Demographic variables included were age, sex, type of valve dysfunction, and interval to diagnosis of valve dysfunction after transplantation. Valvular heart disease was categorized as aortic regurgitation (AR), aortic stenosis (AS), mitral regurgitation (MR), mitral stenosis, pulmonary regurgitation, pulmonary stenosis, TR, tricuspid stenosis, and infective endocarditis. The management options were grouped into four categories: Category A, cardiac surgery excluding retransplant and valve surgery; Category B, valve surgery; Category C, nonsurgical interventions; Category D, conservative management of valve disease.

After the categories were created, the procedures and treatments falling into each category were defined. According to these identifications, Category A was

generated for including composite valve procedure, valve-sparing aortic root replacement, and coronary artery bypass graft surgery in one group, whereas Category B covered surgical bioprosthetic or mechanical valve replacements and valve repair surgery. Category C included nonsurgical interventions of percutaneous coronary intervention (PCI), percutaneous tricuspid valve repair, transcatheter aortic valve replacement, and transcatheter mitral valve repair (TMVR). Category D was composed of patients receiving conservative treatment.

Patients were categorized into the mentioned groups according to the management protocol that applied to them. Moreover, overall death rates were reported per study rather than overall mortality rates associated with individual treatment plans since the high number of case reports may skew the overall mortality rates.

RESULTS

Following the database search, exclusion by abstract, and removal of duplicates, 51 articles were identified and deemed eligible for full-text screening. Of these 51 articles, 18 articles were excluded for the following reasons: 10 included interventions on valves before or during heart transplantation, three had no data on intervention, two had no information on valve disease, two articles did not mention relevant patient outcomes in accordance with the inclusion criteria, and finally, one article did not report any information on heart transplantation. The PRISMA flowchart of the study selection process is reported in Figure 1.

The final number of articles included in the scoping review was 33. Of these, 23 (69.70%) reported a single case and discussed the relevant treatment, nine (27.27%) were retrospective studies, and one (3.03%) paper was a systematic review. The list of articles and their types is displayed in Table 1.

Patient demographics

A total of 13,757 patients (10,529 males, 3,228 females; mean age: 60.3±10.4 years; range, 20 to 83 years) having heart transplantation

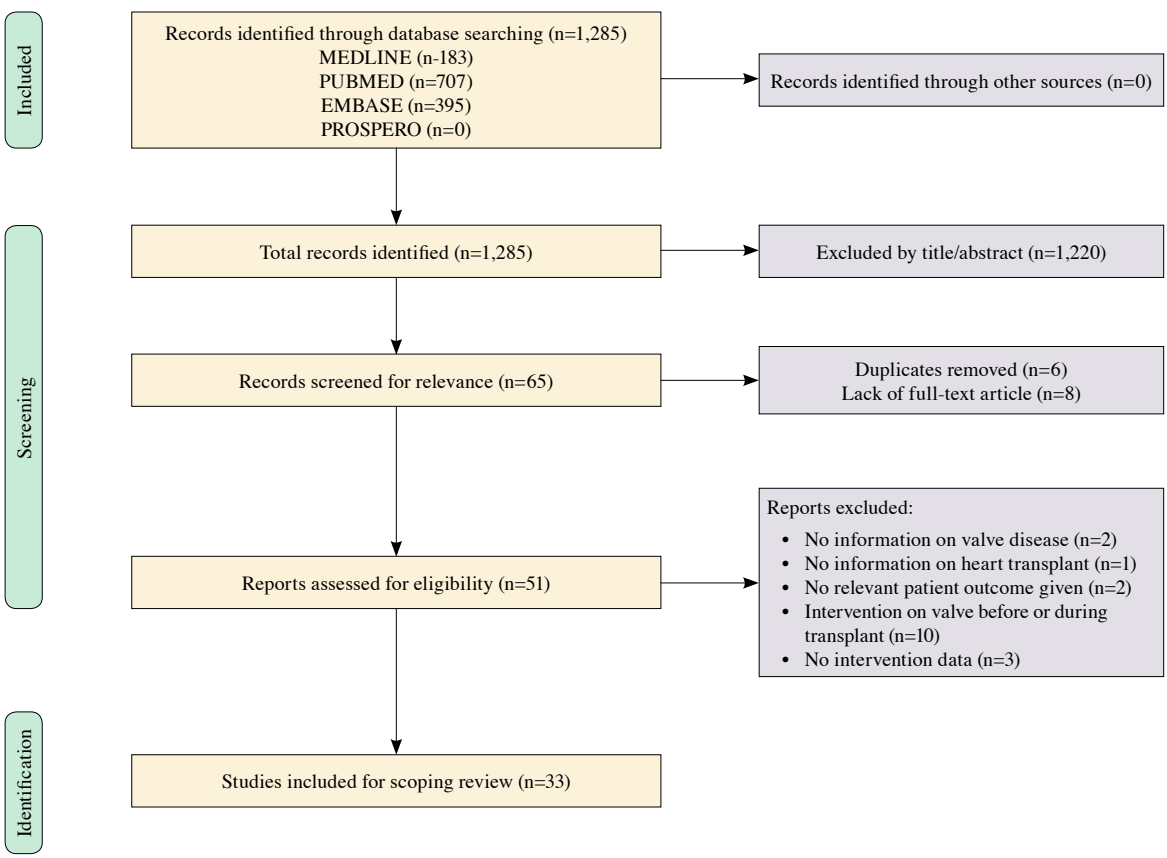

Figure 1. The PRISMA flowchart outlining study selection process.

were reported in the 33 studies included in this review. Out of the total population, 903 (6.56%) patients had one or more valvular disease. The mean interval from the transplant to the diagnosis of valve disease was 11.31±6.95 years. Patients' clinical characteristics are summarized in Table 1.

Table 1. Distribution of publications and patient demographics

Articles	Year	Type of study	Number of patients with heart transplant	Number of patients with valvular disease	Age (mean)	Male (%)	Mean interval to diagnosis of valve dysfunction post-transplant (years)
Campany et al.[40]	2022	Retrospective	2	2	NR	NR	NR
Jordan et al.[43]	2022	Systematic review	57	45	51.29	75.4	NR
Lopez-Vilella et al.[12]	2022	Retrospective	1,009	200	55	78.9	1.94
Martinez-Sellés et al.[44]	2021	Retrospective	8,305	11	57	72.73	8.58
Nersesian et al.[52]	2021	Case report	1	1	53	100	0.63
Roth et al.[11]	2021	Case report	2	2	81.5	NR	26
Wallen et al.[15]	2020	Case report	1	1	80	100	24
Wosten et al.[53]	2020	Case report	1	1	67	100	15
Avula et al.[32]	2019	Case report	1	1	73	100	19
Bishawi et al.[13]	2019	Retrospective	542	542	52	74.7	NR
Farag et al.[22]	2019	Retrospective	479	16	60.7	87.5	6.1
Kremer et al.[54]	2019	Case report	1	1	50	0	10
Salas et al.[25]	2019	Case report	2	2	60.5	100	NR
Akleh et al.[31]	2018	Case report	1	1	77	100	23
Jandhyala et al.[46]	2018	Case report	1	1	59	100	2
Goekler et al.[33]	2017	Retrospective	1,466	7	62.14	85.7	8.15
Margale et al.[35]	2017	Case report	1	1	65	100	12
Stephens et al.[55]	2017	Case report	1	1	60	0	13
Kyranis et al.[34]	2016	Case report	1	1	68	100	12
Gopalamurugan et al.[41]	2014	Case report	1	1	60	100	20
Holmes et al.[6]	2014	Retrospective	912	10	46	80	7.48
Unic et al.[29]	2013	Case report	1	1	50	100	2
Vollroth et al.[56]	2013	Case report	1	1	71	100	15
Zanuttini et al.[30]	2013	Case report	1	1	75	100	14
Elhenawy et al.[28]	2012	Case report	1	1	45	0	17
Bruschi et al.[37]	2010	Case report	1	1	67	100	9
Goerler et al.[19]	2010	Retrospective	819	25	51.5	NR	8.37
Seiffert et al.[36]	2010	Case report	1	1	67	100	14
Joyce et al.[38]	2009	Case report	1	1	55	100	11
Chen et al.[27]	2008	Case report	1	1	64	100	3
Morio et al.[45]	2008	Case report	1	1	53	100	0.13
Wigfield et al.[23]	2008	Case report	1	1	40	100	8.42
Roig et al.[50]	2007	Retrospective	141	20	54	83	7.82

NR: Not reported.

Diagnosis

Tricuspid regurgitation was the most common valve dysfunction, diagnosed on 796 occasions. This was followed by MR in 22 occurrences, AR in 14 occurrences, AS in 11 occurrences, and mitral stenosis in three separate occasions. More than one heart valve dysfunction was observed in some patients concurrently. In addition to aortic valve disease, a bicuspid aortic valve was detected in three patients, of whom one had an aortic root dilation.

Pulmonary valve stenosis, pulmonary valve regurgitation, and tricuspid stenosis were not observed

Table 2. Distribution of valvular diseases and treatment categories

Articles	Year	Diagnosis (no of patients)	Management category
Campany et al.[40]	2022	NR	C: 2
Jordan et al.[43]	2022	21 mitral IE, 12 tricuspid IE, 10 aortic IE, 2 pulmonary IE	A: 5, B: 14, D: 57
Lopez-Vilella et al.[12]	2022	200 TR (moderate-to-severe)	B: 1, C: 1, D: 196
Martinez-Sellés et al.[44]	2021	4 aortic, 4 mitral, 3 tricuspid, 1 pulmonary valve endocarditis	B: 1, D: 11
Nersesian et al.[52]	2021	1 MS (severe)	C: 1
Roth et al.[11]	2021	2 TR (severe)	C: 2
Wallen et al.[15]	2020	1 AS (severe)	C: 1
Wosten et al.[53]	2020	1 TR	C: 1
Avula et al.[32]	2019	1 AS (severe)	C: 1
Bishawi et al.[13]	2019	114 moderate and severe TR, 428 no/trace/mild TR	B: 6, D: 536
Farag et al.[22]	2019	6 MR, 10 TR	A: 1, B: 16
Kremer et al.[54]	2019	1 MS	B: 1
Salas et al.[25]	2019	2 MR (severe)	C: 2
Akleh et al.[31]	2018	1 AS	C: 1
Jandhyala et al.[46]	2018	1 AR (moderate) with MR (severe)	B: 1
Goekler et al.[33]	2017	2 AS, 1 MS, 1 MR, 3 TR	A: 10, B: 7
Margale et al.[35]	2017	1 AS (severe)	C: 1
Stephens et al.[55]	2017	1 AR (moderate)	A&B: 1*
Kyranis et al.[34]	2016	1 AS (severe)	C: 1
Gopalamurugan et al.[41]	2014	1 AR	C: 1
Holmes et al.[6]	2014	1 AS, 3 AR, 2 MR, 5 TR	A: 12, B: 10
Unic et al.[29]	2013	1 aortic valve endocarditis with severe AR	B: 1
Vollroth et al.[56]	2013	1 MR	B: 1
Zanuttini et al.[30]	2013	1 AR (severe)	C: 1
Elhenawy et al.[28]	2012	1 AR (severe) with aortic root and ascending aorta aneurysm	A: 1
Bruschi et al.[37]	2010	1 AS (severe)	C: 1
Goerler et al.[19]	2010	1 IE (aort + mitral + tricuspid), 1 AR, 2 MR, 20 TR	A: 23 B: 25
Seiffert et al.[36]	2010	1 AS (severe)	C: 1
Joyce et al.[38]	2009	1 mild-to-moderate AR, moderate AS	B: 1
Chen et al.[27]	2008	1 severe AR with dilation of aortic root	A&B: 1*
Morio et al.[45]	2008	1 IE (mitral)	D: 1
Wigfield et al.[23]	2008	1 moderate/severe MR with moderate TR	B: 1
Roig et al.[50]	2007	2 AR, 6 MR, 12 TR	B:1, C:2

Management Category A: Cardiac surgery excluding retransplant and valve surgery; B: Valve surgery; C: Non-surgical intervention; D: Conservative management; NR: Not reported; IE: Infective endocarditis; TR: Tricuspid regurgitation; MS: Mitral stenosis; AS: Aortic stenosis; MR: Mitral regurgitation; AR: Aortic regurgitation; * The case had a non-valve cardiac surgery and a valve surgery at the same time.

Table 3. The management and overall death

Articles	Year	Management	Overall death	
			n	%
Campany et al.[40]	2022	2 TAVR	0/2	0
Jordan et al.[43]	2022	2 TV surgery, 7 MV surgery, 5 AV surgery	3/19	15.79
Lopez-Vilella et al.[12]	2022	1 TV annuloplasty, 1 PCI, 196 conservative	88/200	44
Martinez-Sellés et al.[44]	2021	10 Antimicrobial therapy only, 1 MVR + Antimicrobial therapy	5/11	45.45
Nersesian et al.[52]	2021	1 TMVR	0/1	0
Roth et al.[11]	2021	2 PTVR	0/2	0
Wallen et al.[15]	2020	1 TAVR	0/1	0
Wosten et al.[53]	2020	1 PTVR	NR	
Avula et al.[32]	2019	1 TAVR	0/1	0
Bishawi et al.[13]	2019	6 TV repair, 536 no or conservative	9/542	1.66
Farag et al.[22]	2019	5 TVR (1 mechanical, 4 bioprosthetic) 7 TV repair 6 MVR (mechanical)	2/16	12.50
Kremer et al.[54]	2019	1 MVR (bioprosthetic)	0/1	0
Salas et al.[25]	2019	2 TMVR	0/2	0
Akleh et al.[31]	2018	1 TAVR	0/1	0
Jandhyala et al.[46]	2018	1 MVR (bioprosthetic) with AV valvuloplasty	NR	
Goekler et al.[33]	2017	1 TVR (bioprosthetic) 2 TV annuloplasty 1 MVR (mechanical) 1 MV annuloplasty 2 AVR (bioprosthetic)	2/7	28.57
Margale et al.[35]	2017	1 TAVR	0/1	0
Stephens et al.[55]	2017	1 Aortic root replacement with AVR (bioprosthetic)	NR	
Kyranis et al.[34]	2016	1 TAVR	0/1	0
Gopalamurugan et al.[41]	2014	1 TAVR	0/1	0
Holmes et al.[6]	2014	3 TVR (1 mechanical, 2 bioprosthetic) 2 TV repair 1 MVR (bioprosthetic) 1 MV repair 4 Bentall	1/10	10
Unic et al.[29]	2013	1 AVR (bioprosthetic)	NR	
Vollroth et al.[56]	2013	1 MVR (bioprosthetic)	0/1	0
Zanuttini et al.[30]	2013	1 TAVR	NR	
Elhenawy et al.[28]	2012	1 Aortic root replacement	NR	
Bruschi et al.[37]	2010	1 TAVR	0/1	0
Goerler et al.[19]	2010	15 TVR (bioprosthetic) 5 TV repair 2 MVR (not reported on type) 1 MV repair 1 David 3 Aortic root replacement 2 AVR	13/25	52.00
Seiffert et al.[36]	2010	1 TAVR	NR	
Joyce et al.[38]	2009	1 AVR (bioprosthetic)	0/1	0
Chen et al.[27]	2008	1 Bentall with a prosthetic valve conduit	0/1	0
Morio et al.[45]	2008	1 Antifungal therapy	1/1	100
Wigfield et al.[23]	2008	1 MV annuloplasty	0/1	0
Roig et al.[50]	2007	1 MV surgery, 2 PCI	4/6	66.67

TAVR: Transcatheter aortic valve replacement; AV: Aortic valve; TV: Tricuspid valve; PCI: Percutaneous coronary intervention; MVR: Mitral valve replacement; TMVR: Transcatheter mitral valve repair; PTVR: Percutaneous tricuspid valve repair; TVR: Tricuspid valve replacement; AVR: Aortic valve replacement; MV: Mitral valve; PCI: Percutaneous coronary intervention.

in any of the reviewed articles. Additionally, infective endocarditis was identified on 62 occasions, which are ranked in the following order: 27 mitral, 16 tricuspid, 16 aortic, and three pulmonary valve endocarditis. Studies including infective endocarditis also mentioned patients having infection in nonvalvular structures of the heart and pacemakers, but these patients were not included. The distribution of patients with the diagnoses of valve disease, including endocarditis, are summarized in Table 2.

Management

As mentioned above, the management options described in the literature have been divided into categories for simplification. Category A, which is non-retransplant nonvalve surgeries, comprised 54 cases. These operations are listed as valve-sparing aortic root replacement, coronary artery bypass graft, pulmonary artery graft replacement, and pacemaker extraction. Category B is surgical valve repair or replacement applied in 89 operations. The distribution of operations was as follows: there were 49 instances of tricuspid valve replacement or repairs, 26 instances of mitral valve replacement and repairs, and 13 instances of aortic valve replacement and repairs. When inspected in detail, it was recognized that 14 of these operations were performed due to the indication of infective endocarditis.

Category C, which is defined as nonsurgical interventions, occurred in 20 patients and is characterized as follows: 11 of the patients underwent transcatheter aortic valve replacement, and the rest of the nine patients were equally divided between TMVR, percutaneous tricuspid valve repair, and PCI. Moreover, the majority of patients (n=801) were in Category D. The detailed classifications are summarized in Table 2.

In addition to the management options, overall death rates are calculated per study. The management plans and overall death rates per study are summarized in Table 3.

DISCUSSION

This review confirms that valvular disease following heart transplantation is a rare condition. As far as the preliminary search has shown, there is no number available for the occurrence of valvular dysfunction following heart transplantation in the literature. However, the results of this review demonstrate that only 6.56% of cardiac transplant patients experienced valvular dysfunction. It is striking that the percentage is low, and when the reasons for this are investigated, it is found that the patients diagnosed with valvular dysfunction after heart transplantation are not recorded in the International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation.[3] Consequently, underreporting of posttransplant valvular disease must be considered. Furthermore, it has been indicated that there was insufficient information about the surgical treatment of late complications after heart transplantation.[15] Normally, a contraindication to harvest a graft is the presence of any echocardiographic valvular changes, and yet, valve procedures can be performed on marginal donors before the transplantation, and this can help expand the donor pool without affecting outcomes.[16,17] Moreover, it is well-known that valvular dysfunction following cardiac transplantation is not as frequent as CAV, a condition that is responsible for long-term graft dysfunction.[3,18]

Tricuspid regurgitation following cardiac transplantation is the most commonly diagnosed valve dysfunction.[6,19] This can be explained with right heart strain and repeated endomyocardial biopsy. According to Kwon and Shemin,[10] loss of coaptation of the valve results in regurgitation of blood in systole and causes right heart pressures to rise. Furthermore, endomyocardial biopsy is a requirement for screening for graft rejection, and trauma can occur to the chordal tissue during this procedure. This damage can lead to regurgitation and, eventually, right-sided heart failure in case of inadequate treatment. Moreover, López-Vilella et al.[12] demonstrated that timing of TR onset is related to the etiology, and Aziz et al.[20] reported that early development of TR was correlated with allograft rejection and high pulmonary resistance.

The treatment for TR following heart transplantation is primarily medical, but surgical intervention may be needed to achieve functional improvement.[21] In case the competence is due to structural damage, it is challenging to repair; thus, valve replacement is recommended. However, the coaptation defects due to annular dilation can be repaired via ring annuloplasty.[22] To prevent the occurrence of TR, regular echocardiographic follow-ups are crucial to detect early signs of regurgitation and initiate treatment when necessary.[12]

Although the incidence of TR varies in the literature, the data is limited on the dysfunction of other valves.[6,9] When valve diseases other than TR are examined, MR diagnoses are the second most common in the review. It is thought that frequent

biopsy is behind this disease, similar to TR, and it is stated that graft atherosclerosis may also be a cause.[23] As the left ventricle dilates due to ischemia and fibrosis, it causes chordal arrangement to change and restricts mitral valve closure.[7] Although the MR can persist to a mild degree, there is a risk of developing severe MR, and patients with severe MR present with dyspnea and exercise intolerance.[7] There are various options to treat severe MR, either conservatively via minimally invasive interventions or surgery, but the ultimate decision will be made in accordance with patient factors and the clinical presentation. For instance, if the patient has both MR and TR, mitral valve replacement performed concomitantly with intervention for TR would protect from increased TR postoperatively.[24] In this review, the number of patients attending surgical valve replacement or surgical repair of the mitral valve was 26. However, TMVR has become a solid alternative for the management of MR in high-risk patient populations.[25,26]

Another possible valvular dysfunction in this patient population is AR. In this review, AR is identified on 14 occasions, two of which are concomitant with aortic root enlargement, and one of the cases presented includes infective endocarditis.[27-29] The number of occasions was less than TR because left-sided valves are less affected by degenerative processes.[30]

In addition, AS is identified in 11 patients in this review.[6,15,31-38] Two of the patients underwent cardiac transplantation with a graft that has bicuspid aortic valve.[31,38] Bicuspid aortic valve is the most common congenital valvular abnormality in which only two cusps of the aortic valve are present since the separation of valve cusps does not happen in the fetal period.[7,31] Not only can this condition be defined at any age without any clinical findings but it also has a potential to cause stenosis and regurgitation in the aortic valve.[39] Although the appropriate treatment for transplant patients with bicuspid aortic valve is not clearly identified, this review found two different approaches in two different patients. While the first patient with bicuspid aortic valve received aortic valve replacement, the second patient underwent transcatheter aortic valve implantation (TAVI).[31,38] Additionally, there is limited data on the outcomes of TAVI in patients having bicuspid aortic valve; thus, there is no standard treatment that has been established for this condition and its associated valve dysfunction.[38]

Postcardiac transplant patients are at a higher risk for redo cardiac surgery for a number of reasons, such as receiving immunosuppressive therapy and its complications, along with other comorbidities.[25] Thus, nonsurgical interventional procedures may be considered for these patients as an alternative to repeat surgery. This review found 20 patients undergoing these procedures, and 16 of them had these procedures in the last 10 years.[15,30,31,34-37,40,41] Significant developments in nonsurgical interventions, such as with TAVI and TMVR, provide more useful and safer approaches.[25,33,42] Although there are no studies identifying long-term outcomes for heart transplant patients receiving TAVI compared to surgical aortic valve replacement, this procedure can be an alternative for high-risk patients.[31]

In addition to the valvular dysfunction, five articles evaluated for this review reported infective endocarditis on heart valves.[19,29,43-45] Immunosuppressive treatment following cardiac transplant increases the risk of patients having infections requiring challenging management. Martínez-Sellés et al.[44] conducted a review with 8,305 patients with cardiac transplants, and 18 infective endocarditis cases were detected. They also found that the major pathogens were Staphylococcus sp., Enterococcus sp., and Aspergillus. In addition to these five articles, Jandhyala et al.[46] presented a patient infected with *Coxiella burnetti* and he had undergone a mitral valve replacement with an aortic valvuloplasty. However, it is not possible to indicate which microorganism has more incidence in the selected patient cohort for this review.

Alternatively, a dilated aortic root can be replaced with the David procedure.[47] In the review, there was one case report presenting a valve sparing aortic root replacement, but they also replaced the ascending aorta.[28] In terms of comparing these two operations mentioned in the general population, it was found that valve-sparing root replacement has better long-term outcomes and fewer operative deaths.[48]

Another condition that can be seen with valvular heart disease is CAV. Cardiac allograft vasculopathy is characterized by diffuse intimal proliferation, mostly in the distal portions of the coronary artery. The exact reason for occurrence has not been identified, and yet, it is thought that an immunologic response can cause the vasculopathy.[49] In this review, two patients with MR and one patient with TR had undergone PCI due to significant coronary stenosis.[12,50] Information is limited in terms of the relation between valve dysfunction and CAV. However, a pathologic study of allograft hearts has showed that two out of

64 allografts had end-stage valvular disease.[49] Moreover, patients with cardiac transplantation need to be closely followed to identify CAV and prevent its complications.

The main limitation of this review is the small number of studies reporting patients with valvular disease after heart transplantation. In addition, most of the studies were case reports, which are considered low-level evidence.[51] Furthermore, the articles excluded during the literature search may have included information relevant to this review. This research review was carried out by two authors, which may cause selection bias.

In conclusion, due to the longer survival following heart transplantation, there is a higher likelihood of experiencing more complications. One of these complications is valvular heart disease, which can be seen in this patient group even though it is less frequent. The lack of patients presenting with this condition is a challenge to ensure timely, appropriate, and adequate treatment, which can be grouped as surgical, nonsurgical, or conservative. Consequently, it is not possible to indicate which treatment method is superior according to the extracted data unless more information is obtained from the databases.

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