Tricuspid valve regurgitation in heart transplant patients

Dimčić, Tjaša

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Tjaša Dimčić

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GRADUATE THESIS

Zagreb, 2019.

This graduation thesis was made at the Department of cardiovascular diseases, University hospital centre Zagreb, mentored by Asst. Prof. Boško Skorić and was submitted for evaluation in the 2018/2019 academic year.

Statistics was performed by dr. Pero Hrabač.

Abbreviations

TVR – tricuspid valve regurgitation

TR – tricuspid regurgitation

HTx – heart transplantation

BMI – body mass index

TV – tricuspid valve

PH – pulmonary hypertension

RV – right ventricle

LV – left ventricle

EMB – endomyocardial biopsy

ICM – ischemic cardiomyopathy

DCM – dilative cardiomyopathy

ECHO – echocardiography

mPAP – mean pulmonary arterial pressure

PVR – pulmonary vascular resistance

TPG – transpulmonary pressure gradient

PCWP – pulmonary capillary wedge pressure

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1. SUMMARY

Tricuspid valve regurgitation in heart transplant patients – Tjaša Dimčić

Introduction: Tricuspid valve regurgitation (TVR) is a multifactorial and the most common valve disease in cardiac transplant patients. In most cases TVR is mild and with no clinical importance, but some cases of moderate or severe TVR are related with significant morbidity and mortality. It seems that the lowest prevalence of TVR is 3 years after heart transplantation.

Aim: To measure the prevalence of TVR after heart transplantation in our patients and its association with different variables related to both the donor and the recipient of the heart transplant. The analysed recipient variables were age, gender, body mass index, aetiology of heart failure prior to transplantation and pre-transplant hemodynamic status (pulmonary vascular resistance, mean pulmonary arterial pressure, pulmonary capillary wedge pressure and transpulmonary gradient). The donor variables were age and gender. Lastly, we tested an association of ischemic time of the heart and the number of biopsies in post-transplant graft rejection surveillance with the development of TVR.

Materials and methods: In this single centre retrospective study we included 135 patients that had undergone heart transplantation in the University Hospital Centre Zagreb in the period between 2008 and 2016, and were followed up for a time period of 3 years by echocardiographic examination. They were divided into those with no or trivial TVR and those with at least mild TVR. These groups were compared according to the above-mentioned variables. The statistical analysis was performed using SPSS statistical software.

Results: 23% of the patients were female and 77% were male. The average age of the recipients and donors were 52 and 38, respectively. 53% of the patients had an above normal BMI. The prevalence of mild TVR was 27%, moderate 2% and there was only one patient with severe TVR. The analysis showed no association between donor age and gender with severe TVR. There was also no association of TVR with recipient age, gender, body mass index, aetiology of heart failure prior to transplantation, or pre-transplant hemodynamic status (pulmonary vascular resistance, mean pulmonary arterial pressure, pulmonary capillary wedge pressure and transpulmonary gradient). The average number of biopsies per patient was 15. There was no association between the number of biopsies in patients with no/trivial and at least mild TVR.

Conclusion: The prevalence of TVR in our heart transplant patients is very low, with only 2% diagnosed with moderate TVR. We have not found any correlation between the tested variables and TVR despite them being reported in other literature. A possible explanation, besides the relatively low number of patients in the study, is the low number of biopsies and the long sheath technique for taking the biopsies, which spares the tricuspid valve from potential injury.

Key words: Tricuspid valve regurgitation, heart transplantation, donor, recipient

2. SAŽETAK

Trikuspidalna regurgitacija srca kot transplantirnih pacienta – Tjaša Dimčić

Uvod: Trikupidna regurgitacija (TR) je multifaktorijalna i najčešća valvularna greška u bolesnika nakon transplantacija srca. U većini slučajeva TR je blaga i klinički neznačajna, ali u nekih je bolesnika umejerena ili teška i povezana sa značajnim simptomima i povećanom smrtnosti. Čini se, da je najmanja pojavnost ove greške u trećoj godini nakon transplantacije.
Cilj: Odrediti prevalenciju TR u naših bolesnika nakon transplantacije srca i moguću povezanost ove greške sa nizom varijabli donora i primatelja srčanog presatka. Analizirane varijable primatelja bile su: dob, spol, indeks tjelesne mase, etiologija srčanog popuštanja prije transplantacije i prijetransplantacijski hemodinamski status bolesnika (plućna vaskularna rezistencija, srednji tlak u plućnoj arteriji, okluzivni plićni tlak i transpulmonarni gradijent). Analizirane varijable donora uključivale su dob i spol. Također, ispitali smo moguću povezanost novonastale TR i trajanja ishemije presatka, te ukupnog broja biopsija endomiokarda učinjenih u svrhu detekcije odbacivanja presatka kroz period praćenja.
Materijal i metode: U ovu retrospektivno studiju uključili smo 135 bolesnika kojima je u period između 2008. i 2016. Godine učinjena transplantacija srca u Kliničkom bolničkom centru Zagreb u koji su ultrazvočnu evaluirani nakon tri godine od transplantacije srca. Bolesnike smo podijelili na skupinu bez ili sa trivijalnom TR, i skupinu s minimalno blagom TR. Ove skupine bolesnika su potom uspoređene prema gore navedenim karakteristikama. Statistička analiza učinjena je SPSS softwaru.
Rezultati: Bilo je ukupno 23% ženskih i 77% muških primatelja. Prosječna dob primatelja iznosila je 52 godine, a donora 38 godina. Povišeni BMI našli smo u 53% bolesnika. Pojavnost blage TR iznosila je 27% umjerene TR 2%, dok je samo jedan bolesnik imao tešku TR. Nismo našli povezanosti između TR i starosti ili spola donora. Također, nismo našli povezanosti TR sad obi, spolom, BMI, etiologijom srčanog popuštanja prije transplantacije i prijetransplantacijskim hemodinamskim statusom bolesnika (plućna vaskularna rezistencija, srednji tlak u plućnoj arteriji, okluzivni plućni tlak i transpulmonalni gradijent). Prosječno je bilo 15 biopsija po bolesniku u navedenom period praćenja. Nije bilo razlike u broju biopsija između bolesnika bez/sa trivijalnom TR i bolesnika sa minimalno blagom TR.
Zaključak: Učestalost TR u bolesnika nakon transplantacije srca u našem centru je vrlo niska, sa samo oko 2% bolesnika sa barem umjerenom težinom greške. Za razliko od opažanja objavljenih u literature nismo našli povezanost niti jedne ispitivane varijable sa TR. Moguće objašnjenje, osim relativno malog broja ispitnika uključenih u ispitivanje, je i u relativno malom broju učinjenih biopsija i tehnici izvođenja biopsije koja koristi dugo uvodnicu pri čemu teoretski smanjuje močućnost mehaničke ozljede ovog zalistka bioptomom.

Ključne riječi: Trikuspidna regurgitacija, transplantacija srca, donor, primatelj

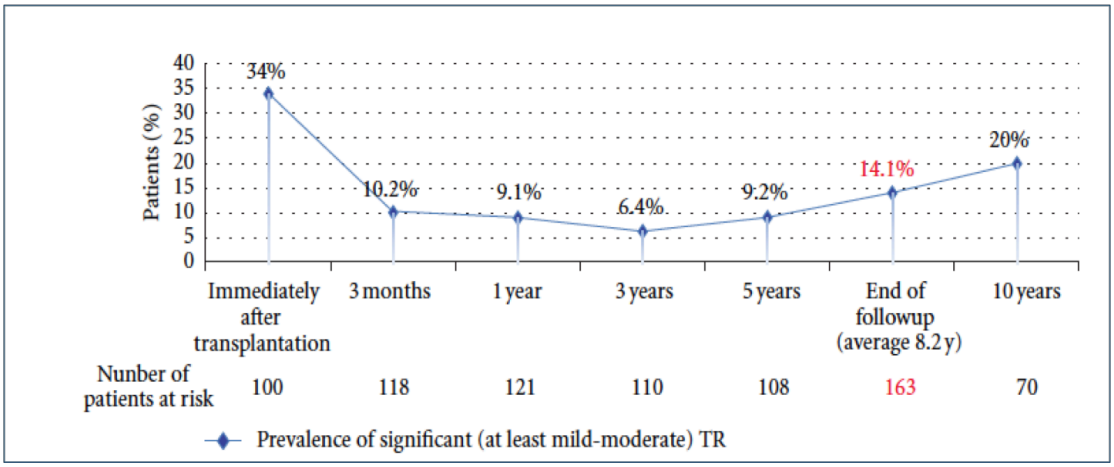
3. PREFACE

3.1 TRICUSPID VALVE REGURGITATION

TVR is the most common valvular complication after heart transplantation (HTx). In a healthy individual, TVR is often present as a trivial finding, and it is not considered as a risk factor for heart problems. One of the reasons for the development of TVR is that a new heart needs to accommodate to the new body with physiological changes that affect valve closure. Surgical technique, whether bi-caval or bi-atrial, can pose a potential threat to the development of the TVR. Secondly, the transplanted heart being too small for the size of the recipient may have an impact. Moreover, in the period between explantation and transplantation, i.e. during the ischemic time, the heart is exposed to certain changes of the tissue. There is also possible effect of the hemodynamic conditions in the recipient that the donor heart has to adapt after transplantion. It is also questionable whether a cause of heart failure prior to transplantation may affect the development of TVR. Lastly, for a post-transplant patient follow-up in terms of potential organ rejection, a certain number of biopsies need to be taken. The biopsy technique can also have an effect on the TVR, since the every introduction of the bioptome in the right ventricle across the tricuspid valve exposes the valve to possible mechanical injury. Graft rejection as well might potentially cause papillary muscle edema with consequent TVR.

3.1.1 PREVALANCE

The prevalence and severity of TR change during the post-transplantation period. In most cases TR is mild and asymptomatic, but some cases of moderate or severe TR are related to morbidity and mortality. [1-5] Significant TR prevalence peaks immediately after transplantation (34% of patients), decreases to nadir (6.4%) after 3 years, and then increased gradually. [6] Doppler echocardiography is the most common technique used for detection and evaluation of the severity of TR. [7,8]



Berger et al. J Transplant 2012; 2012:120702 [6]

3.1.2 ETIOLOGY

3.1.2.1 Functional tricuspid valve regurgitation

Like in the native heart, TVR in the cardiac allograft has both functional and anatomic causes. One of the predominant mechanisms of the former is geometric distortion of the tricuspid annulus often influenced at the time of transplantation. [9] There are the two surgical techniques of heart transplantation: bi-atrial and bi-caval. The surgical technique seems to influence the occurrence of tricuspid regurgitation because of the alteration of right atrial morphology with bi-caval technique related to better outcome. Bi-caval technique was used in patients included in our study. The enlarged right atrial size of the combined atria in the bi-atrial technique was thought to exacerbate the development of TVR by increasing both wall tension and tricuspid annular size during systole. [10] However, a tension in the bi-caval anastomosis is considered a risk factor for the development of TVR as stretching of the right atrium may results in distortion of the tricuspid annulus. [9] Echocardiographic assessment of patients with tricuspid regurgitation and PH demonstrates that the RV not only dilates, but also increases in length along the superior-inferior axis leading to valvular tethering and reduced coaptation. [11] Increased episodes of acute rejection greater than ISHLT Grade 2 was also correlated to increase TVR due to mechanism of papillary muscle edema and dysfuntion as well as asymmetric contractility of the RV. [12]

3.1.2.2 Anatomic tricuspid valve regurgitation

Studies have demonstrated a causal link between the number of endomyocardial biopsies (EMB) and the development of TVR. EMB is the current standard of care in routine graft surveillance and is used more frequently especially in the early time period following transplantation. Chordal damage resulting in flail leaflets is the presumed mechanism and development of TVR. [9] In one report, there were no cases of severe TVR in patients who have had fever than 18 biopsies whereas in patients with over 31 procedures 60% developed severe TVR. [13]

Another anatomic cause of TVR is endocarditis. Although this is relatively unusual type of infection, it has been reported that the incidence of infective endocarditis among HTx recipients was 50/110-fold higher than in general population. [9, 14, 15] Possible causes include catheter-related and other nosocomial blood stream infections, LV assist device-related mediastinitis, donor heart contamination, deep wound infections following transplant, EMB and suppression of cell-mediated immunity. [16]

3.1.3 HEART BIOPSIES

EMB (endomyocardial biopsy) remains the gold standard for monitoring and diagnosing allograft rejection after orthopic heart transplant. [13] EMB protocol in the Clinical Hospital Centre Zagreb during the first year is the following: first EMB is performed as following: 1st month after HTx, 2nd month, 4th month, 6th month, 9th month and 12th month, which makes the total number of biopsies 6.

After that the biopsies are taken in time of 1 year and 4 months, 1 year and 8 months, 2 years, 2 years and 6 months, 3 years, 4 years and 5 years. Additional biopsies are performed when clinical suspicion of graft rejection was raised.
Further biopsies were performed when clinical suspicion of graft rejection was raised. Biopsies were evaluated for rejection using the ISHLT (International Society of Heart and Lung Transplantation) criteria. [22]

Any additional EMB might be performed in case of rejection of the previous biopsy. The total number of yearly EMBs performed in the Clinical hospital centre Zagreb is half of the protocol of Berger er al. J Transplant. [6]

EMB may be performed with two different techniques. The first includes percutaneous right internal jugular vein approach with use of a short sheath 12 cm in length, while the second technique uses a long sheath 96 cm in length that is inserted through femoral vein. With the transjugular technique, a bioptome is introduced directly over tricuspid valve into the right ventricle, while with the transfemoral approach a long sheath is introduced into the right ventricle over a wire after loading with a Pigtail catheter and the bioptome is then introduced without direct contact with the tricuspid valve. With both approaches, the bioptome is directed under fluoroscopy toward the interventricular septum, where 3-4 samples are taken.

3.1.4 CLINICAL PRESENTATION OF TVR IN THE HEART RECIPIENT

Regurgitation of blood from right ventricle to right atrium during systole leads to the combination of elevated right-sided pressures as well as decreased cardiac output. Increased right atrial pressure in severe TVR results in venous congestion with clinical sequelae of acites, peripheral edema and hepato-renal dysfunction. Over time, the volume and pressure overload lead to the worsening of RV function with a further decrement in cardiac output that can be difficult to differ from graft rejection.

When functional TVR is a consequence of left sided heart disease, shortness of breath, exercise intolerance, orthopnea and physical finding of lung congestion will be present as well.

3.1.5 EVALUATION OF TVR

The severity of TVR after the third year was evaluated with echocardiography, where patients were categorized into no symptoms, mild, mild-to-moderate and moderate-to-severe TVR. This was assessed by comparing the ratio of TR jet area to the right atrial area on color Doppler and was scored from 0-3: 0 – 0.5 was no to trivial TVR, 1 was mild TVR, 1.5 - 2 was moderate TVR and 2.5 - 3 was severe TVR.

3.1.6 MANAGEMENT

Symptomatic TVR is first treated with medications. Diuretic therapy with furosemide is indicated - usual doses are 40-160 mg daily. Spironolactone appears to be especially useful in patients with TVR and right ventricular failure with doses of 25-100 mg daily. If this is not sufficient, severe TVR may be treated with valve surgery. [24]

Multiple studies have shown that the majority of TVR that develops following heart transplantation does not lead to symptoms significant enough to warrant surgical repair. [6, 24, 25] In the minority of patients, however, for whom TVR leads to medically refractory symptoms, repair and replacement options have been employed. [9]

Replacement is associated with improving symptoms and seems to have the added benefit of durability when compared to repair options. [26] With regards to valve type, mechanical valves would be undesirable due to the inability to perform subsequent EMBs and the need for anticoagulation. The biologic valves, on the other hand, appear to have excellent long-term durability in the low-pressure system of the right heart, do not require anticoagulation, and afford on-going ability to perform biopsies. [9]

4. HYPOTHESIS

The prevalence of TVR in our heart transplant patients may be related to donor age as well as recipient age and BMI. TVR may be related to prolonged time of ischemia, unfavourable pre-transplant hemodynamic and a large number of biopsies performed for the post transplant surveillance of graft rejection.

5. OBJECTIVES

We have performed a retrospective analysis of 135 consecutive patients that underwent heart transplantation at the University Clinical Hospital Centre Rebro in the period between 1.1.2008 and 1.1.2016, to analyse the prevalence of post-transplant tricuspid valve regurgitation and its possible correlation with various clinical risk factors.

6. MATERIAL AND METHODS

In this single-centre retrospective study we included all consecutive patients with heart transplantations from the University Clinical Hospital Centre Zagreb in the period between 1.1.2008 and 1.1.2016.

Two-dimensional and colour Doppler echocardiography studies were performed on an annual basis with 2.5-MHz phrased-array sector scanner in the HTx patient 3-years post-transplant. Multiple views of the tricuspid valve were examined to assess for TR. Severity of TR was assessed by comparing the ratio of TR jet area to the right atrial area on color Doppler and was scored from no or trivial TVR, mild TVR, moderate TVR and severe TVR.

Categorical data are presented as absolute and relative frequencies, continuous variables as median with range. Results are introduced in the form of tables and graphs. Statistical significance was set at $P < 0,05$. For the statistical analysis of the of data we used the application SPSS for Windows 17.0 and Microsoft Excel (version 11 Microsoft Corporation, Redmond, WA, SAD).

7. RESULTS

There are 135 patients that undergone heart transplantation in the period of 1.1.2008 - 1.1.2016 in the University Clinical centre Rebro Zagreb in Croatia.

Each patient was retrospectively followed up for severity of TVR for 3-years. There were 23% of patients without TVR, 43% with slight TVR, 32% with mild TVR and only 1% with moderate TVR and 1% with severe.

1. TVR and donor age

There was no significant difference in TVR after HTx in relation to donor age (Man-Whitney, $p = 0.977$). The average age of the donors was 38 years. The youngest donor was 12 and the oldest was 60 years old. The donors were younger in comparison to the recipients ($p < 0.001$, Man-Whitney test).

2. TVR and donor gender

70% of the donors were male and 30% were female. There was no significant difference in TVR after HTx with regard to donor gender (Chi-square, $p = 0.141$).

3. TVR and recipient age

There was no significant difference in TVR after HTx with respect to the age of the recipient (Man-Whitney, $p = 0.325$).
The average age of the recipients was 52 years. The youngest patient was 15 and the oldest 70 years old.

4. TVR and recipient gender

There was no significant difference in TVR after HTx with respect to the gender of the recipient (Chi-Square, p = 0.228). 77% were male recipients and 23% were female recipients. There were more female recipients with TVR (mild or moderate), but this difference was not statistically significant.

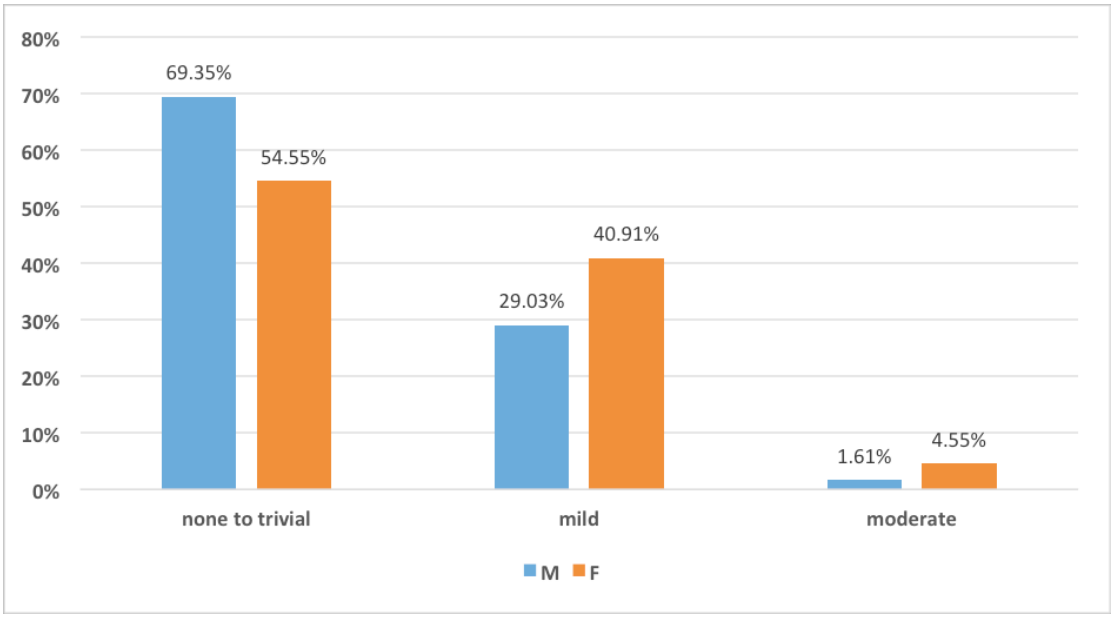


Figure 1: Severity of TVR after HTx with respect to the gender of the recipient.

5. TVR and time of ischemia

The time of ischemia was not related to TVR (Man-Whitney - p = 0.648). The time of ischemia presented as quartiles was also not significantly related with post-transplant TVR (Chi-square test, p = 0.983). The minimal ischemic time was 80 minutes and the maximum was 292 minutes, respectively.

TR and ischemic time	M	N	Min	Max
none to trivial	175,98	49	80,00	292,00
mild	181,90	20	81,00	283,00
moderate	247,00	1	247,00	247,00
All Grps	178,69	70	80,00	292,00

Table 1: Time of ischemia presented as quartiles in relation with post-transplant TVR.

6. TVR and pre-transplant hemodynamic parameters

There was no significant difference in pretransplant mPAP (p = 0.487), PVR (p = 0.768), TPG (0.893) and PCWP (p = 0.638) among patients with and without posttransplant TVR at 3 years.

The median of PCWP for those without and for those with TVR was 25 mmHg and 26 mmHg, respectively. The median of TPG was 8 mmHg for both groups. The median of PVR for those without and for those with TVR was 161 mmHg and 168 mmHg, respectively. The median of mPAP without TVR was 32 mmHg, and 38 mmHg with TVR.

7. TVR and number of biopsies in the first 3 years

The number of biopsies in the first three years after transplantation was not different among patients with and without TVR (p = 0.188).
The minimal number of biopsies was 4 and the maximum was 29, with the median value of 15 biopsies.

8. TR and type of cardiomyopathy

There was no significant difference in TR after HTx with regard to the etiology of heart failure before HTx (Chi-square, p = 0.806).

The majority of patients had dilative cardiomyopathy (51%), followed by patients with ischemic origin of cardiomyopathy (35%). The rest of them had other types of cardiomyopathies such as restrictive and valvular, or congenital heart disease (14%).

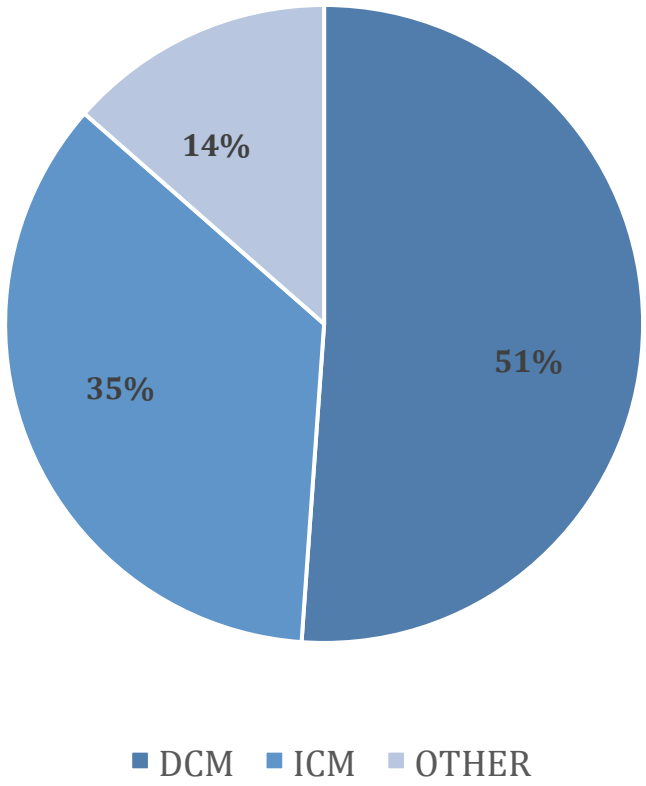


Figure 2: Etiology of heart failure before HTx.

9. TR and BMI of donor

The pre-transplant BMI was normal in 42,2% of recipients. 4.4% of patients with BMI lower than normal. 22,2% of patients were obese, and 31,1% of patients had a BMI of more than 30, indicating severe obesity.

There was no significant difference in TR after HTx with regard to the donors' BMIs (Man-Whitney, p = 0.155).

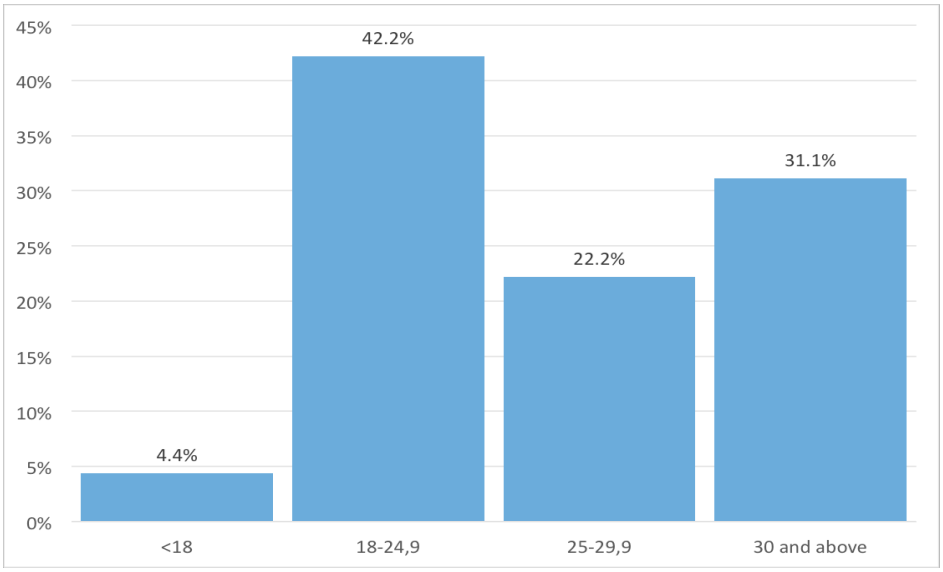


Figure 3: Pre-transplant BMI in recipients of donor hearts

8. DISCUSSION

Tricuspid valve regurgitation is the most common valvular disease in heart transplant patients. The nadir of prevalence is in the 3rd year after transplantation, when significant TVR was reported in 6% of patients, and significant TVR was defined as at least mild to moderate. [6] In our patients, the prevalence of TVR, defined as at least mild was very low at 32%, and only 1% had moderate TVR. It is possible that the bi-caval surgical technique of transplantation that was solely used, the low number of biopsies as well as biopsy technique are responsible for this observation.

We have not found any relation between post-transplant TVR and the recipients' age, gender, body mass index, aetiology of heart failure prior to transplantation and pre-transplant hemodynamic status (pulmonary vascular resistance, pulmonary arterial pressure, pulmonary capillary wedge pressure and trans-pulmonary gradient). There was also no correlation with the age or gender of the donor, or with the ischaemic time of the heart.

Lastly, we have not found association between and the number of biopsies performed during the follow-up period. Our patients had an average of 15 biopsies during three post-transplant years. This relatively low number of biopsies along with the long-sheath technique with low potential for peri-procedural tricuspid valve damage may explain the low prevalence of post-transplant TVR in our patients.

The limitations of our study include its retrospective nature and the relatively low number of patients included in the follow-up.

9. CONCLUSION

1. TVR has very low prevalence in our patients after heart transplantation. This prevalence is significantly lower than reported in literature.

2. Post-transplant TVR in our patients was not related to recipient age, gender, body mass index, aetiology of pre-transplant heart failure as well as pre-transplant hemodynamic status (pulmonary vascular resistance, mean pulmonary arterial pressure, pulmonary capillary wedge pressure and trans-pulmonary gradient).

3. Post-transplant TVR in our patients was not related to donor age and gender.

4. Post-transplant TVR in our patients was not related to the number of performed biopsies.

In conclusion, although TVR is the most common heart valve disease reported in cardiac transplant patients, we have found a very low prevalence of this disease in our population of transplant patients. We have not found any correlation between post-transplant TVR and different both recipient and donor-related characteristics. Because the bi-caval technique was the only technique used in study patients, we could not compare the effect of surgical techniques on post-transplant TVR. The number of biopsies in the follow-up did not affect the occurrence of TVR. This may be explained by the low number of biopsies, as well as the biopsy technique that use long-sheath and preserves the tricuspid valve from potential mechanical damage.

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