Cardiovascular interventions in Marfan syndrome: the early and late results

Marfan sendromunda kardiyovasküler girişimler: Erken ve geç dönem sonuçları

Adil Polat,[1] İlker Mataracı,[2] Ebru Bal Polat,[3] Berk Özkaynak,[1] Bülent Mert,[1] Kaan Kırali,[2] Vedat Erentuğ,[1] Rahmi Zeybek,[2] Cevat Yakut[2]

[1]Department of Cardiovascular Surgery, Bağcılar Training and Research Hospital, İstanbul;
[2]Department of Cardiovascular Surgery, Kartal Koşuyolu Heart Education and Research Hospital, İstanbul;
[3]Department of Cardiovascular Surgery, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul

Background: In this study, we analyzed the risk factors for early and late results in the patients with Marfan syndrome who underwent surgery in our clinic.

Methods: Between February 1987 and October 2008, 62 patients with Marfan syndrome (45 males, 17 females; mean age 31.5±9.9 years; range 11 to 56 years) underwent surgery. A total of 90 surgical interventions were performed on these patients. Univariate and multivariate analyses of the risk factors were performed to evaluate the effect of these interventions on survival.

Results: Mean follow-up was 7.9±4.2 (range 0.2 to 17.4) years, giving a total follow-up of 471.2 patient/years. Early mortality was reported in two of the patients (3.2%). Survival rates at one, six and 15 years were 96.8±2.2%, 94.4±3.2% and 87.1±5.8%, respectively. None of the risk factors were significantly associated with the early mortality. Univariate analysis of risk factors showed that emergency surgery and re-surgery were significantly associated with late mortality ($p<0.05$), whereas multivariate analysis demonstrated that only emergency surgery ($p<0.05$) was significantly associated with late mortality. At 15 years, new aneursym, dissection-free and mitral regurgitation-free survival rates were 73.5±9.7%, 93.2±4.9%, 87.3±8.7%, respectively.

Conclusion: Our study results suggested improved survival associated with surgical intervention, while showing reduced life expectancy in the patients with Marfan syndrome who underwent emergency surgery. Therefore, those patients should be monitored for cardiovascular involvement carefully.

Key words: Long-term results; Marfan syndrome; surgery.

Amaç: Bu çalışmada kliniğimizde ameliyat edilen Marfan sendromlu hastaların erken ve geç dönem sonuçları için risk faktörleri analiz edildi.

Çalışma planı: Şubat 1987 - Ekim 2008 tarihleri arasında kliniğimizde Marfan sendromlu 62 hasta (45 erkek 17 kadın; ort. yaş 31.5±9.9 yıl; dağılım 11-56 yıl) ameliyat edildi. Bu hastalara toplam 90 cerrahi işlem uygulandı. Cerrahinin sağkalım üzerindeki etkisini değerlendirmek amacıyla, bu risk faktörlerinin tek değişkenli ve çok değişkenli analizleri yapıldı.

Bulgular: Ortalama takip süresi 7.9±4.2 (dağılım 0.2-17.4) yıl olup, toplam 471.2 hasta/yıl idi. İki hastada (%3.2) erken mortalite bildirildi. Bir, altı ve 15 yıllık sağkalım oranları sırasıyla, %96.8±2.2, %94.4±3.2 ve %87.1±5.8 idi. Hiçbir risk faktörü erken mortalite ile anlamlı düzeyde ilişkili bulunmadı. Geç mortalite için yapılan tek değişkenli analizde, acil ameliyat ve tekrar ameliyat mortalite ile ilişkili bulunurken, çok değişkenli analizde yalnızca acil ameliyat mortalite için anlamlı bir risk faktörüydü. Yeni anevrizma ve diseksiyon gelişimi ile mitral yetmezlik olmadan 15. yılda sağkalım oranı, sırasıyla %73.5±9.7, %93.2±4.9 ve %87.3±8.7 idi.

Sonuç: Çalışma sonuçlarımız, cerrahi tedavi ile sağkalımda iyileşme olduğunu göstermekle birlikte, acil ameliyata alınan hastaların yaşam beklentisinde düşüş olduğunu göstermiştir. Bu nedenle, Marfan sendromlu hastalar kardiyovasküler tutulum açısından dikkatle izlenmelidir.

Anahtar sözcükler: Geç dönem sonuçlar; Marfan sendromu; cerrahi.

Received: November 3, 2010 *Accepted*: March 5, 2011

Correspondence: Adil Polat, M.D. Bağcılar Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Kliniği, 34200 Bağcılar, İstanbul, Turkey.
Tel: +90 212 - 440 40 00 e-mail: adilpol@yahoo.com

Marfan syndrome is an autosomal dominant connective tissue disease which affects cardiovascular, skeletal, and ocular systems. The incidence is reported to be from four to 17 for every 100,000.[1,2] The disease is fatal because of progressive dilatation in the proximal aorta followed by dissection and rupture, which decreases life expectancy to below 40 years of age in its natural course.[2] In order to increase life expectancy, cardiovascular complications must be addressed and corrected in a timely manner.

Since our facility is known as one of the major cardiac centers in our country, many Marfan syndrome patients have been referred to our clinic over the years. We retrospectively reviewed our experience and analyzed the early and long-term results of the operations performed for these cases.

PATIENTS AND METHODS

We collected patient data from the hospital records. All patients were in a regular follow-up program in our hospital's outpatient care facility. No patients were lost to follow-up, and they all had regular hospital visits and required postoperative tests when necessary. Telephone interviews with the patients in this follow-up were conducted before the final analysis. Informed consent was obtained from all of the patients before the operations.

Demographic data

In Koşuyolu Heart and Research Hospital, between February 1987 and October 2008, 62 Marfan patients (45 males, 17 females; mean age 31.5±9.9 years; range 11 to 56 years) were operated on for cardiovascular pathology. The male to female ratio was 2.7:1,

Preoperative risk factors

All of the patients analyzed had been diagnosed before their hospitalization for Marfan syndrome. Preoperatively, a positive family history for Marfan syndrome was present in 11 patients (20%), hypertension in nine (14.5%), coronary artery disease and pulmonary dysfunction in two (3.2%), and renal dysfunction in one patient (1.6%). No abnormalities of the aortic valve, such as bicuspid valve, were found.

Statistical methods

Patient data was organized and grouped with Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) for Windows version 11.0. Continuous variables were expressed as average ± standard deviation (SD), and the ranges of the data were also given. Ratios were presented as percentages (%). Univariate analysis was applied to the following parameters for how they relate to mortality: preoperative factors (age, sex, presence of an acute aortic dissection, chronic aortic dissection, ascending aortic aneurysm, mitral regurgitation, family history, hypertension, preoperative renal dysfunction, preoperative left ventricular dysfunction with an ejection fraction (EF) <40%, and emergency operation), intraoperative and postoperative factors (use of deep hypothermic circulatory arrest along with postoperative revision surgery for bleeding), and post-discharge factors (reoperation, recently developed aortic aneurysm, aortic dissection, and mitral regurgitation). For univariate and multivariate analyses, a p value of <0.05 was accepted as significant. Survival periods were expressed as average ± standard error (SE). Life tables were compared according to risk factors, and the differences were analyzed with the Cox regression test. Parameters with p<0.10 were removed. After the analyses, p<0.05 was accepted as significant. A logistic regression test was used to compare two-tailed results, and p<0.05 was accepted as significant.

Cardiovascular complications and indications for surgery

Forty-six patients (74.2%) had aortic regurgitation, and 42 (67.7%) had an ascending aortic aneurysm with an average diameter of 7.0±1.9 cm. The indication for the aortic aneurysm was a diameter above 4.0-4.5 cm. The surgical indications for the first operations are summarized in Table 1. The indications for surgery in aortic and mitral regurgitation (>grade 3) were given according to the American Heart Association valvular guidelines.[3] Concomitant to these diagnoses, two patients had atrial septal defect (ASD), and one patient had tricuspid regurgitation. Patients who had undergone two or more operations had been previously analyzed.[4] Acute aortic dissection denoted dissection confined to the aorta and presenting within 14 days from the onset of symptoms. Chronic aortic dissection denoted dissection

Table 1. Surgical indications in the initial operations

Indication	n	%
AAA + AR	33	53.2
Acute dissection + AR	6	9.7
Acute dissection	5	8.1
Mitral regurgitation	5	8.1
AAA + acute dissection	3	4.8
AAA + acute dissection + AR	3	4.8
AAA + chronic dissection + AR	2	3.2
Chronic dissection	2	3.2
AAA + chronic dissection	1	1.6
Chronic dissection + AR	1	1.6
Aortic regurgitation	1	1.6

AAA: Ascending aortic aneurysm; AR: Aortic regurgitation.

Table 2. Surgical procedures

Procedures	n	%*
Flanged Bentall-De bono procedure	37	59.7
Bentall-De bono procedure	8	12.9
Ascending aortic replacement	8	12.9
Elephant trunk procedure	5	8.1
Hemiarcus replacement	5	8.1
Aortic arcus replacement	3	4.8
Descending aortic replacement	3	4.8
Thoracoabdominal aortic replacement	3	4.8
Aortobifemoral bypass	1	1.6
Mitral valve replacement	8	12.9
Mitral Repair	4	6.5
Aortic valve replacement	2	3.2
Atrial septal defect repair	2	3.2
Tricuspid DeVega annuloplasty	1	1.6
Total	90	

* Percent of patients who had the procedure.

confined to the aorta and presenting after 14 days from the onset of symptoms. Aortic and mitral regurgitation denotes severe failure of the aortic valve (>grade 2).

Procedures

Cardiopulmonary bypass was instituted by ascending aortic cannulation. When this was not possible, femoral arterial cannulation was performed. Bicaval or femoral venous cannulation was also implemented. Femoral arterial and venous cannulation was used in four operations, all of which were reoperations. We performed deep hypothermic circulatory arrest (DHCA) in all 21 patients who had thoracoabdominal and aortic arch replacements and in 13 of the aortic root replacements. It was also used in aortic root replacements for dissection. Twelve of these patients had ascending aortic aneurysms, 17 had acute, and three had chronic aortic dissections. Cerebral protection was maintained by retrograde cerebroplegia and topical ice bags, as we have previously reported.[5] We preserved the myocardium with retrograde cardioplegia in most of the cases. Only in patients who had isolated mitral valve procedures did we use antegrade cardioplegia. We did not use aprotinin intraoperatively or postoperatively in any of the cases.

Ninety operations were performed on these 62 patients. Twenty-two operations were performed for nine patients (13 reoperations in total) during their follow-up period. Among these 90 operations, the most commonly performed procedure was aortic root replacement (45 patients, 72.6%). Thirty-seven patients (59.7%) were operated on for the flanged modification of Bentall-De Bono procedure.[6] A composite conduit graft with a mechanical valve was used in the aortic root replacements. Anticoagulation regimens were discussed with the patients before the operations.

Varying degrees of extensive aortic disease were addressed in 20 patients (32.3%) with different segments of aortic replacements. Of the 12 patients (19.4%) with mitral valve disease, eight had valve replacement and four had mitral annuloplasty. Ten had a mitral procedure performed in their first operations. Of these 10 patients, five had surgery only for the mitral disease whereas the other five had concomitant aortic root replacement.

Surgical procedures are listed in Table 2 and procedures performed on reoperated patients are summarized in Table 3.[4] Seventeen patients (27.4%) had surgery on an emergent basis due to aortic dissection.

Follow-up

The post-discharge follow-up was conducted in our hospital's outpatient clinic. The follow-up schedule was every three months during their first postoperative year and then annually afterwards. Computed tomography/magnetic resonance imaging (CT/MRI) scanning was performed on those patients who had aortic replacements. Cardiac and valvular functions were evaluated with transthoracic echocardiography.

Table 3. Reoperations

Patient	Initial operation	Second operation	Third operation
1	Bentall + ETP	MVR	–
2	Flanged Bentall	Arcus AR	–
3	Flanged Bentall†	TAA + AR	MVR (33 Carbomedics, BL)
4	Flanged Bentall + mitral RA	Descending AR	TAA + AR
5	Flanged Bentall	TAA + AR	–
6	Aortobifemoral bypass	Hemiarcus AR	TAA wrapping
7	Flanged Bentall	TAA + AR	–
8	MVR (31 Sorin, BL)	Ascending AR	–
9	Descending AR	TAA + AR	TAA + AR

† Concomitant atrial septal defect repair; RA: Ring annuloplasty; MVR: Mitral valve replacement; AR: Aorta replacement; TAA: Thoracoabdominal aorta; ETP: Elephant trunk procedure.

Table 4. Postoperative morbidity

Morbidity	n	%
Arrhythmia	11	17.7
Infection	6	9.7
Pulmonary dysfunction	5	8.1
Renal dysfunction	2	3.2
Bleeding	2	3.2
Low cardiac output syndrome	1	1.6
Transient neurologic dysfunction	1	1.6

RESULTS

Postoperative morbidity

Postoperative morbidity is listed in Table 4. As can be seen from the table, the most commonly encountered complication was arrhythmia. These patients responded well to antiarrhythmic therapy, and in only one patient did ventricular arrhythmia persist. Of the four patients who showed postoperative renal dysfunction, two had normal renal function preoperatively.

Postoperative mortality

In-hospital mortality was 3.2% with two male patients, a 24-year-old and a 26-year-old. Both had ascending aortic aneurysms and aortic regurgitation (6.3 and 10 cm respectively) and left ventricular dysfunction. Both patients had a flanged modification of the Bentall-De Bono procedure. Postoperative mortality was due to low cardiac output in both cases. Four patients (6.9%) died in the follow-up period. One of them was a male patient who had a flanged Bentall procedure. In his ninth postoperative year, he died of a ruptured descending aortic aneurysm. Two young, male patients who underwent a modification of the Bentall procedure using the Carrel button technique[5] had sudden cardiac death in their 18th and 11th postoperative years. The other late term mortality was in a female patient who was operated on at 54 years of age. She died of pneumonia in her hometown in the postoperative sixth year.

Survival rates for one, six and 15 years were 96.8±2.2%, 94.4±3.2%, and 87.1±5.8% respectively (Figure 1). After univariate analysis, no risk factor significantly affecting early mortality could be identified. The risk factors for late mortality were emergency operations (p=0.0001) and reoperations (p=0.0001). As the survival rates were compared, patients who had emergency operations showed significantly worse survival rates than the patients who underwent elective procedures (98.3±0.1% vs. 87.50±11.70%; p=0.02). Survival rates were not significantly different between the patients who underwent reoperations during their follow-up and those who did not (95.2±0.2% vs. 90.0±0.1%; p=0.90). Survival rates after reoperations were 95.56±3.04%, 90.66±4.40% and 60.32±12.63% for one, five and 10 years respectively, as was determined by the Cox regression analysis. The mean duration for survival for the reoperated patients was 112±18 months [72-127 months, 95% confidence interval (CI)].

After univariate analyses, multivariate analyses were performed (Table 5). Emergency operations constituted a risk factor for late mortality (p=0.03) whereas reoperations were not significantly related with late mortality. The only factor which was significantly related to the mortality after the analysis with logistic regression was recently developed dissection [odds ratio (OR)=3.8712; p=0.0065].

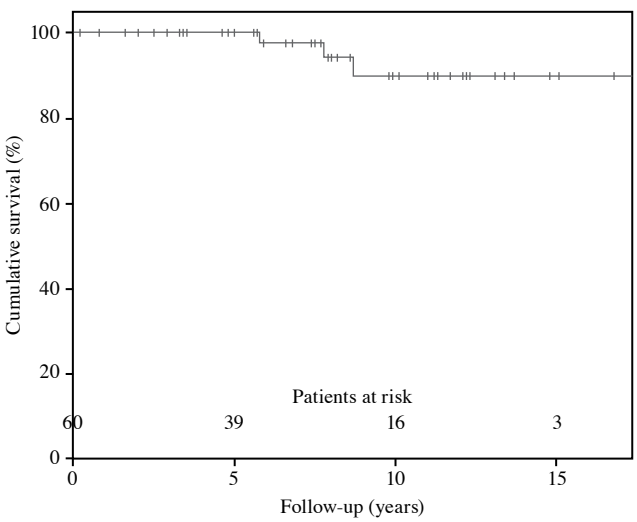

Figure 1. Survival curve.

Table 5. Results of univariate analysis

Characteristics	n	%	*p*
Age <30 (years)	25	40.3	0.852
Male	45	72.6	0.653
Acute aortic dissection	17	27.4	0.586
Chronic aortic dissection	8	12.9	0.324
Ascending aortic aneurysm	42	67.7	0.602
Mitral regurgitation	12	19.4	0.350
Family history	11	17.7	0.630
Hypertension	9	14.5	0.850
Preoperative renal dysfunction	1	1.6	0.809
Preoperative LVD (EF <40%)	10	16.1	0.677
Emergency operation	17	27.4	0.0001
Reoperation	9*	14.5	0.0001

* Number of patients who had reoperation; LVD: Left ventricular dysfunction; EF: Ejection fraction.

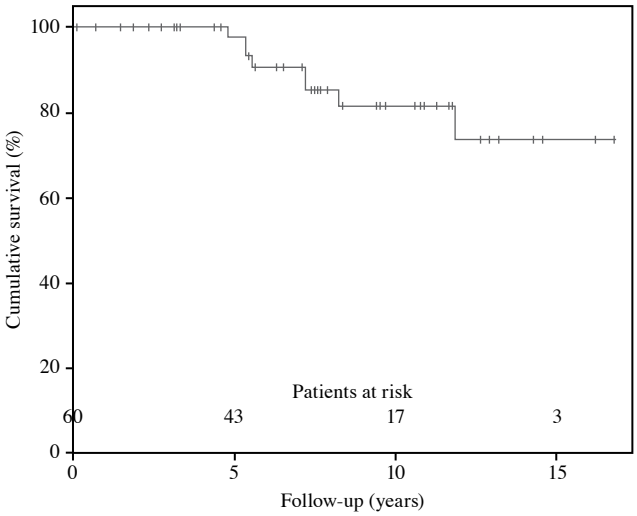

Figure 2. Survival free from new aneurysm.

Follow-up

After discharge, patients were followed up in our hospital outpatient clinic. The average follow-up duration was 7.9±4.2 (0.2-17.4) years adding up to a total of 471.2 patient years. The survival rate for patients who were free of new aneurysms at one, five and 15 years was 100%, 97.7±2.2% and 73.5±9.7% respectively (Figure 2). Additionally, the survival rate for those free of new dissection at one, five and 15 years was 97.7±2.3%, 97.7±2.3% and 93.2±4.9% respectively (Figure 3). Finally, the survival rate for those free of mitral regurgitation at five, 10 and 15 years was 100%, 95.2±4.6% and 87.3±8.7% respectively (Figure 4). We have previously shown that survival rate for patients who were free of reoperation at 13, 24, and 123 months was 95.56±3.04%, 90.66±4.40%, and 60.32±12.63% respectively.[4]

DISCUSSION

Since there is a variable penetration and expression of the disease, survival in Marfan syndrome is mostly related to cardiovascular complications.[2] The systemic involvements, other than the cardiovascular system, are usually not life-threatening. Replacement of the aortic root and ascending aorta with reimplantation of the coronary arteries in the Bentall-De Bono procedure[1,2] and different modifications are used in order to decrease the early surgical and late complications of this procedure. Generally, the surgical cut-off is about 5 cm[7,8] diameter for the aortic root whereas the surgical approach has become more radical with the surgical limit being decreased to 4 cm.[9] According to a risk stratification method proposed by Ergin et al.,[10] in a Marfan patient under 40 years of age with a body surface area of 2 cm^2, 1.3 index will account for 4.2 cm diameter. This approach has decreased the traditional operation limit from 5 cm down to about 4 cm.

Replacement of the ascending aorta and aortic valve with a composite graft and reimplantation of the coronary arteries is the gold standard for aortic root aneurysms in Marfan patients. Other indications for surgery are acute and chronic aortic dissection, severe aortic regurgitation, and progressively increasing dilatation of the aortic root in serial measurements.[2] Acute dissection in the ascending aorta mandates emergent surgery.[2] The decision to operate must be made considering dissection and patient related factors in descending aortic dissections.[11] Aortic regurgitation must be addressed appropriately in Marfan patients. The general surgical indications for aortic regurgitation are relevant for Marfan patients. In patients with an enlarged aortic root, composite graft replacement of that root may be preferred.

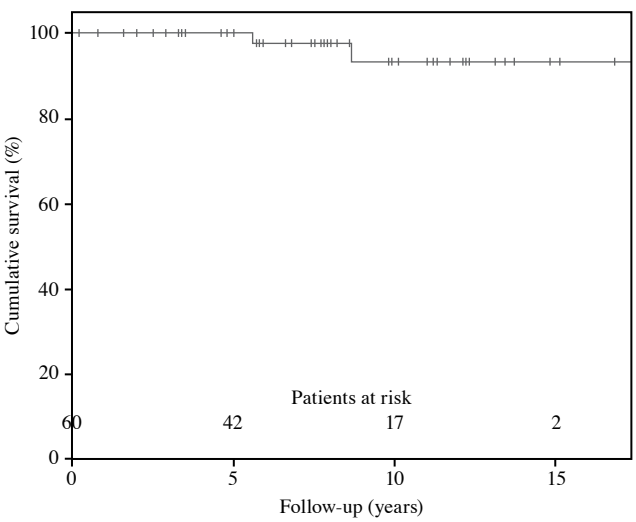

Figure 3. Survival free from new dissection.

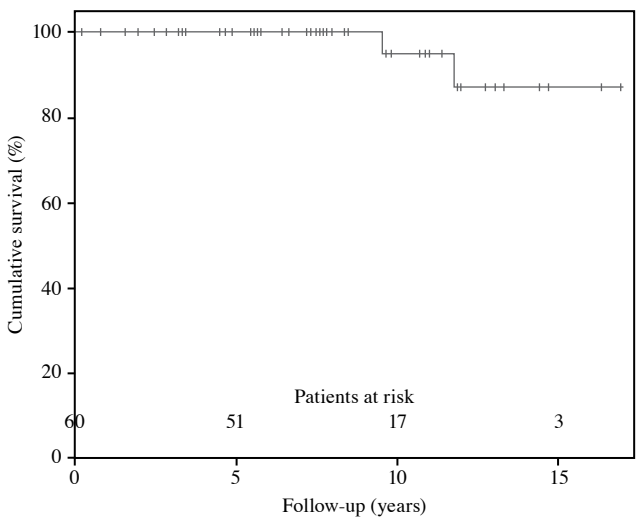

Figure 4. Survival free from new mitral regurgitation.

If the arch is preserved in the aortic root operation, moderate hypothermia will be sufficient. We used DHCA in 21 patients who has surgery mainly for the aortic arch. There were 13 patients operated on with DHCA who had aortic root operations; however, the surgical exposure was important in those operations. In our clinic, we prefer the flanged modification of the Bentall-De Bono procedure as it is suitable for the aortic annulus geometry and physiology.[6,12] It can be seen in the procedures listed in Table 2 that two patients had aortic valve replacements rather than a composite graft replacement. Although we did not detect a new aneurysmal dilatation in our patients, a careful follow-up is required and this factor should be kept in mind in order to plan the reoperation. Aortic dilatation above 4 cm mandates operation. When the arch and descending aorta are affected, all of the affected tissue must be removed.[2] Erentuğ et al.[2] advise medical follow-up in cases in which the aorta is dilated throughout its length.

The key question in operation planning is about timing. The risk of aortic rupture is correlated with the aortic diameter. Aneurysms in patients other than those with Marfan syndrome yield a 10% rupture risk for a diameter over 6 cm.[13] More than a 5% increase in aortic root annually increases the complication risk fourfold.[14]

Another cardiac dysfunction seen in Marfan patients involves mitral valve anomalies. The most common of these anomalies are annular dilatation, fibromyxomatous changes in the leaflets and the chordae, chordal elongation, and calcium deposits.[15] Mitral prolapse is evident in 60 to 80% of all patients secondary to chordal elongation. Mitral valve involvement must be addressed adequately and be assessed with aortic pathologies for timing and choice of surgery. It was discovered in our study that mitral problems were more common than previously thought. Almost half of the mitral patients in our series had no problems in the aorta or other systems. For long-term follow-up of these patients, reoperations must be carefully planned. It may be argued that the inclusion of the operations for isolated mitral valve procedures may alter the statistics slightly, but as we studied the overall cardiovascular management and long-term survival of these patients, their involvement was necessary.

When mitral regurgitation is present together with aortic root or aortic valvular pathology, the timing of the operation becomes complicated. Surgery may be concomitantly performed with the aortic procedure.[13] Surgery is recommended in grade 2 or higher aortic regurgitation, but reconstructive surgery is a matter of debate.[2] It can be seen in Table 2 that of the 12 mitral procedures, eight were replacements and four were valvular repairs. Despite some authors' recommendations in favor of reconstruction, a structural defect was present in these patients which could have hampered the leaflet in the future. In younger patients, reconstruction will avoid anticoagulation requirement, so it may be the operation of choice. In our analysis of mortality, the type of mitral operation was not considered a risk factor; therefore, instead of strict rules, an individually tailored approach may be preferred for mitral procedures in Marfan patients.

After our analysis of the long-term follow-up of Marfan patients, it can be seen that elective operations must be preferred. Emergency operations may be avoided with close follow-up and more liberal operation indications. With elective surgery, morbidity will also decrease, and the long-term results will be even better. Nine of the 62 patients had reoperations. The estimated mean survival is about eight years, which mandates a careful follow-up.[4]

Earlier diagnosis of Marfan patients and a careful follow-up must be made in a cardiovascular clinic. Risk factors should be determined, and general practitioners must be aware of any complication related to this syndrome. In a transition period when the social security is under reconstruction, the course of these patients must be well known and cost, risk analysis, and loss or gain of labor must be made clear to the security companies. Our results indicate a favorable long-term prognosis. One late mortality was due to a ruptured descending aortic aneurysm which could have been prevented by timely surgery. The survival of Marfan syndrome patients could easily be increased with closer and more careful follow-up. The patient follow-up has been completed in this analysis, so these results are important in order to make inferences.

Life expectancy has increased significantly after aortic root replacement.[5] In another Marfan paper, being a male and having emergency surgery were found to be risk factors for mortality.[8] Although emergent surgery was also a factor in our analysis, being a male did not have an impact on the outcome. Considering the dismal effect of new dissections on survival, surgical indications may be more radical in Marfan patients. We have previously reported our experience on the aortic root replacements covering 15 years of follow-up.[16] It can be seen from that study that Marfan syndrome does not affect in-hospital mortality; however, it is associated with a higher risk for long-term mortality.

Pediatric patients were low in number in our series. Of our two patients, one had her child diagnosed with mitral valve prolapse, and he was put into follow-up in our clinic. This shows the importance of family

screening in Marfan patients. As we found no dismal affect of family history on survival, these patients may benefit from earlier diagnosis. However, it may be argued that there is a low family history in this patient cohort. Although all the patients met the criteria for Marfan diagnosis, the family screening may be incomplete due to the socioeconomic status of the patients. Although some patients reported some premature deaths in their families, these cases were not included as Marfan syndrome due to the poor quality of their family histories.

Another limitation may be the absence of aortic valvular reconstruction in our series. We did not perform this procedure in Marfan patients. As this procedure becomes more common, we are carefully examining the clinical results. Despite the increasing numbers of reports of successful reconstruction results,[17] there are controversial series, like that of Zehr et al.[18] which report high reoperation and failure rates. Fleischer et al.[19] showed that the aortic and mitral cusps are as equally affected as the aortic wall. Considering the reoperation possibility that already exists in a Marfan patient, this could be considered an excessive risk.

The lack of yearly morbidity data, such as information regarding thromboembolisms or hemorrhagic events in patients who had the Bentall procedure, in the study is a result of a problem with the patient files. Although we had some postoperative follow-up values, the outpatient clinic files were not regularly recorded, and some of the patients with complications were admitted to other hospitals, as we discovered afterwards through phone calls. As a result, we excluded these parameters from our analysis to avoid any miscalculations. We did not histopathologically examine the resected specimens. This could be argued as a point of confirmation for the diagnosis of Marfan syndrome. However, all patients were advised of the family screening, and they were admitted to the genetic departments in tertiary clinics where available.

In conclusion, we are sure that our experience with aortic surgery is the key to our success with Marfan patients. Recently, mitral problems have seemed to increase and mandate surgery. First-step health utilities are important for earlier detection of Marfan syndrome and later follow-up and treatment may be continued in a specialized clinic. This will decrease emergency operations and, together with careful follow-up, will further increase life expectancy.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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