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Ten-Year Epidemiological Review of In-Hospital Patients with Marfan Syndrome

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Marfan syndrome is a connective tissue disorder with a worldwide prevalence of 1 in 5,000, without any racial predilection. Major cardiovascular manifestations of Marfan disease often require surgical intervention. The aim of this study was to examine the demographics of patients with Marfan syndrome admitted to Hong Kong hospitals over a 10-year period from 1997 to 2006. We retrospectively reviewed the prospectively collected Hong Kong Health Authority's Clinical Data Analysis and Reporting System and Clinical Medical System. Statistical analysis was performed using SPSS, version 15. A total of 525 patients with Marfan syndrome (310 male, 215 female) were included in this study. For males, mean age at first hospital admission was 19.8 years (range 0-78) and for females, 18.7 years (range 0-60). One hundred and twelve (21.3%) patients (56 male, 56 female) had documented aortoiliac aneurysms and/or dissection, with 74 (66.7%) cases involving the thoracic aorta. Forty-nine (9.3%) patients had major cardiac or aortoiliac operations, with an operative mortality of 5/49 (10.2%). Thirty-seven (7.0%) patients (23 male, 14 female) died during this period, with a mean age at death of 41.0 years (range 0-83) for males and 29.9 years (range 0-59) for females. The majority of these patients died of cardiovascular causes, with four aortic dissections, two ruptured aneurysms, seven with sudden collapse and cardiac arrest, and five with heart failure. In addition, there were other causes of mortality: five perioperative, one congenital, and four pulmonary causes, three with malignancy and one of stroke. The cause of death was unknown in five patients. Patients with aortoiliac diseases have a statistically significant higher mortality rate ($p < 0.05$). This population-based study shows that significant numbers of patients with Marfan syndrome are admitted to hospital per year, with a significant proportion requiring admissions at a young age. Life span in Marfan patients is markedly shortened, and aortoiliac disease is probably underdiagnosed. A standardized diagnostic and therapeutic follow-up program should be offered to these patients and their families.

INTRODUCTION

First described by Antoine Marfan in 1896,[1] Marfan syndrome is a connective tissue disorder caused by a mutation in the fibrillin-1 (*FBN1*) gene on chromosome 15, which determines the structure of fibrillin. More than 550 mutations in the fibrillin-1 gene have been identified worldwide;[2] the mutation is not always fully penetrant, and patients may not be diagnosed until later in life.[3-5] There is also significant genetic heterogeneity in that some individuals with marfanoid phenotype have mutations in the *TGFBR1* (transforming growth factor-ß receptor 1) or *TGFBR2* gene.[6] It has been estimated that approximately 1 in 5,000 in the United States has Marfan syndrome.[7] Marfan syndrome does not have a particular gender, racial, geographic, or ethnic predilection.[8,9]

The life expectancy of patients with Marfan syndrome has increased from a mean age at death of 32 in 1972 to 41 in 1993,[7] due to better understanding of the disease process, closer follow-up protocols, active medical management, and advances in cardiac and vascular surgical technology.[10] Despite the proven genetic links of Marfan syndrome, there is

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often a lack of standardized genetic screening and counseling service offered to patients' families.[11] There are studies to show that sudden cardiovascular deaths in first-degree relatives of patients with Marfan syndrome may be avoidable by careful preparticipation screening.[12,13] In a screening of 29,067 children in China, Sun et al.[14] found that the prevalence of Marfan disease was 17.2 per 100,000 of the Chinese population. In a review of 564 patients with Marfan syndrome from 18 provinces and cities in China over a 37-year period, 74.3% of the patients had a strong positive family history. Again, there seems to be a lack of diagnostic and therapeutic follow-up for patients with Marfan syndrome and their families.

The aim of the study was to determine the epidemiology and demographics of patients with Marfan syndrome who were admitted to hospitals in Hong Kong over a 10-year period from 1997 to 2006.

METHODS

The demographics of patients, clinical presentation, management plans, and outcomes for patients with Marfan syndrome in Hong Kong were analyzed using the prospectively collected data in the Hong Kong Health Authority's Clinical Data Analysis and Reporting System (CDARS). CDARS is a comprehensive, prospectively entered, centralized, computerized database for patients admitted to all public Hong Kong hospitals. Codes from the *International Classification of Diseases, 9th Revision, Clinical Modification* were used. All data from public hospital admissions in Hong Kong during the period from January 1997 to December 2006 were retrieved through this computerized database. All in-patient admissions during the study period were included, and some patients required multiple admissions.

Cases were searched using the Clinical Medical System (CMS) for relevant data on cardiovascular (cardiac and aortoiliac) diseases, in terms of conservative or surgical management. Medication in particular beta-blockers was documented. For those patients who underwent surgical intervention, perioperative mortality and period after operation were recorded. For all the Marfan patients, potential risk factors and causes of death were documented.

Survival was calculated using Kaplan-Meier survival curves analysis. The Mantel-Cox log rank test was used to test for statistically significant differences.[15] Statistical analysis was performed using SPSS, version 15.0 (SPSS, Inc., Chicago, IL). $p < 0.05$ was considered statistically significant.

RESULTS

Demographics, Mortality, Morbidity, Surgery, Aortic Surgery

A total of 525 patients with Marfan syndrome (310 male, 215 female) were admitted to various hospitals in Hong Kong. For male patients, the mean age at first hospital admission was 19.8 years, with a range of 0-78. For female patients, the mean age at admission was 18.7 years, with a range of 0-60. There was no statistically significant difference between males and females in survival (Fig. 1).

There were 112 (21.3%) patients (56 male, 56 female) who had documented aortoiliac aneurysms and/or aortoiliac dissection, with 74 (66.7%) cases involving the thoracic aorta. Patients with aortoiliac disease had a statistically significant mortality risk ($p < 0.05$) (Fig. 2). Forty-nine (9.3%) patients had major cardiac or aortoiliac operations, with an operative mortality of 5/49 (10.2%) in the study period (Table I). In the short follow-up period, having aortoiliac surgery did not confer a survival benefit (Fig. 3). The first patient was a 50-year-old female who underwent emergency aortic valvular and ascending aortic replacement with inclusion of the coronary artery (Bentall operation) for acute type A aortic dissection with coronary artery involvement. The heart failed to start and the patient died as she was not able to come off the cardiopulmonary bypass despite a technically successful operation. The second patient was a 53-year-old male who underwent emergency open repair of a ruptured thoracoabdominal aortic aneurysm (type B aortic dissection) and died on the table due to massive bleeding. The third patient was a 47-year-old male with a previous Bentall operation and mitral valve replacement who underwent elective open repair of a 7.1 cm type B thoracic dissecting aneurysm. This patient died on postoperative day 1 due to generalized bleeding and multiorgan failure. The fourth patient was a 22-year-old female who had a Bentall operation and mitral valve valvuloplasty for aortic root dilatation as well as aortic and mitral regurgitation. She required emergency sternotomy on postoperative day 1 and died on postoperative day 2 of coagulopathy as well as cardiopulmonary and multiorgan failure despite maximum inotropic support. The fifth patient was a 15-year-old female with a previous aortic root replacement for aneurysmal disease who underwent elective total aortic arch replacement and elephant trunk operation; she died 5 weeks postoperatively of multiorgan failure. Three other patients died 5, 7, and 29 months

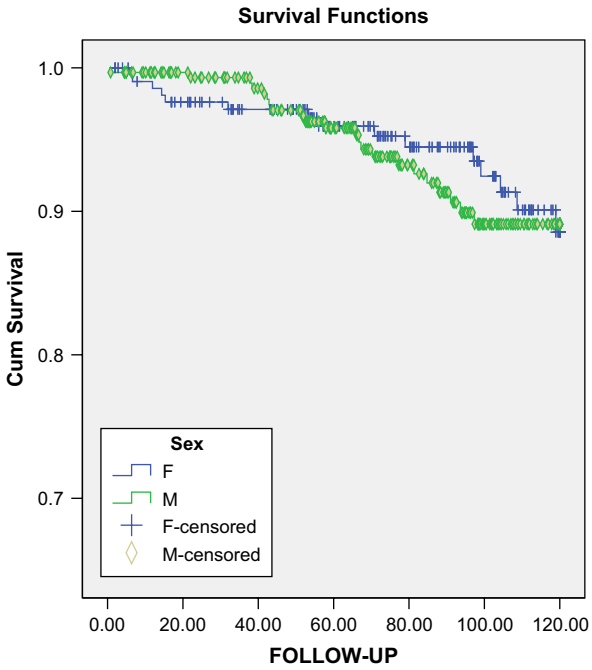

Fig. 1. Kaplan-Meier curves of survival in 310 males and 215 females. A total of 22 males and 15 females died during this period. There was no statistically significant difference between the survival of the two sexes.

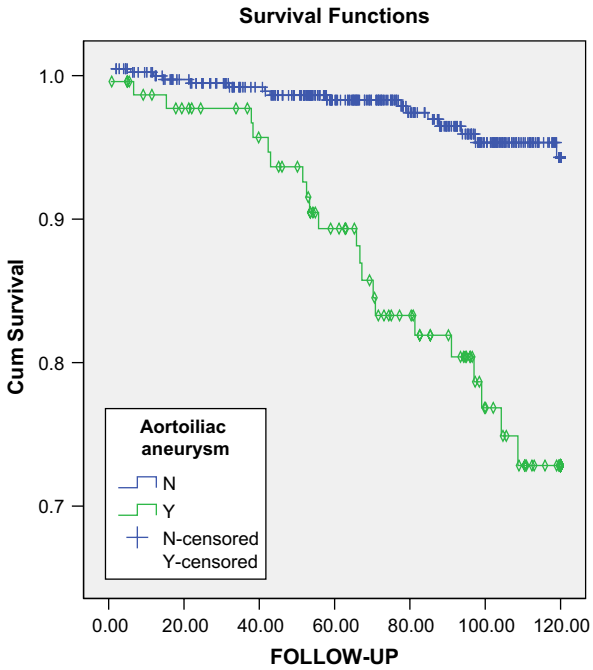

Fig. 2. Kaplan-Meier survival curves in 112 patients with documented aortoiliac disease and 413 patients without documented aortoiliac disease. Aortoiliac aneurysm/dissection is associated with a worse survival outcome ($p < 0.01$).

postoperatively of unrelated causes. Six patients had more than one operation in this 10-year period.

A total of 37 (7.0%) patients (23 male, 14 female) died during this period (including perioperative mortality), with a mean age at death of 41.0 years (range 0-83) for males and 29.9 years (range 0-59) for females (Table II). The majority of these patients died of cardiovascular causes, with four aortic dissections, two ruptured aneurysms, seven with sudden collapse and cardiac arrest, and five heart failures. From the database, we were unable to find out the precise cause of death in the seven patients who developed sudden collapse and cardiac arrest. There were five perioperative mortalities. There were one congenital and four pulmonary causes, three with malignancy and one of stroke. Unfortunately, the cause of death was unknown in five patients.

Our data show that only 128 out of 525 patients, representing 24.4% of the study population), were on beta-blockade medication. Paradoxically, patients on beta-blockers have a worse survival outcome (Fig. 4, Table III).

Table I. Type of surgery in 49 patients

Operation	*n*
Bentall operation	28
Aortic root replacement	7
Aortic valve replacement	4
Mitral valve replacement	3
Aortic arch repair	5
Thoracoabdominal aneurysm repair	5
Infrarenal aortic aneurysm repair	2
Endovascular thoracic stent graft	3

DISCUSSION

This is the first epidemiological study of patients with Marfan syndrome in Hong Kong. We are unsure of the true prevalence of Marfan syndrome in Hong Kong. Only 525 patients were identified from this database, but the population of Hong Kong was about 6.9 million in 2005 (prevalence of 7.6 per 100,000). This is lower than the prevalence of 17.2 per 100,000 in China quoted by Sun et al.[14] and certainly lower than the 1 per 5,000 in United States. Our study relied heavily on the accuracy of prospective data entry in the CDARS, and individual cases were searched using the CMS. We think this is a genuine reflection of the lack of diagnosis of patients with Marfan syndrome, rather than data entry mismanagement. Compared to publication more than a decade ago,[7] the overall mortality was 7%, peaking in the second and fourth decades of life. The majority of our patients had regular

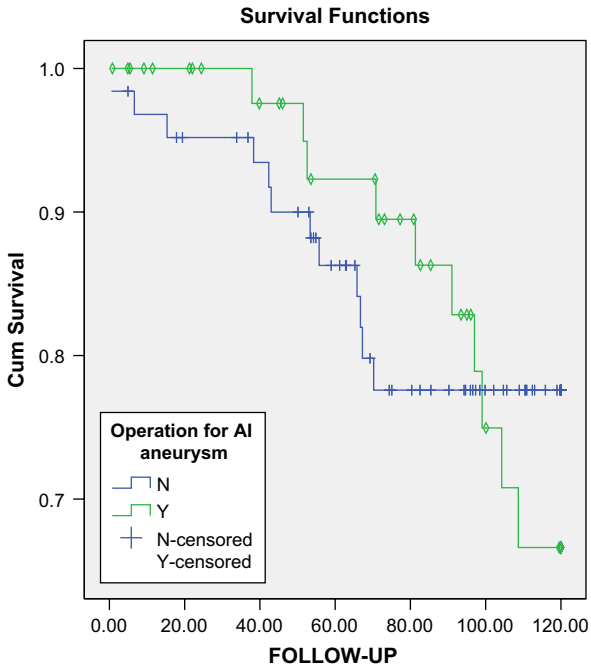

Fig. 3. Kaplan-Meier survival curves in 49 patients who had aortoiliac surgery and in 63 patients who had documented aortoiliac disease but did not undergo surgery. There was no survival benefit to having surgery ($p = 0.934$). AI, aortoiliac.

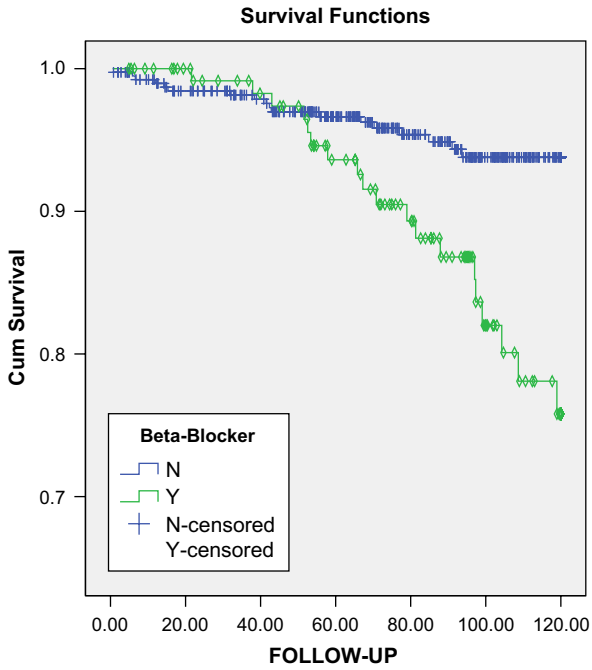

Fig. 4. Kaplan-Meier survival curves in 128 patients taking beta-blockers and 397 patients not taking beta-blockers. Paradoxically, those patients on beta-blockers were associated with a worse survival outcome ($p < 0.01$).

Table II. Cause of death in 37 patients

Aortic dissection	4
Ruptured aneurysm	2
Sudden collapse/arrest	7
Cardiac failure	5
Perioperative	5
Congenital	1
Pulmonary	4
Malignancy	3
Stroke	1
Unknown	5

Table III. Number of patients on beta-blockade medication (128/525 = 24.4%)

Atenolol	33
Carvedilol	13
Esmolol	2
Labetalol	30
Metoprolol	96
Propanolol	19
Sotalol	10

clinical follow-up and adjustment of medication; however, there is no uniform follow-up imaging protocol, irrespective of whether the patient had previously undergone cardiac and aortic surgery.

For patients with a strong family history of Marfan syndrome, it is now advocated that early diagnosis, meticulous echocardiographic/computed tomographic (CT) follow-up, and multidisciplinary assessment are essential in order to prevent cardiovascular complications.[16]

The current literature suggests that screening programs for patients with Marfan syndrome involving genetic professionals such as geneticists and genetic counselors should be considered in order to prevent early mortality. All family members potentially at risk should receive genetic counseling, lifestyle modification advice, and regular clinical and radiological follow-up. It has been shown previously that emergency surgery and history of aortic complications in first-degree relatives are associated with a higher mortality.[17]

Chronic beta-blocker therapy may slow the rate of aortic dilation and may be associated with more favorable prognosis. Unfortunately, we are unable to demonstrate the effect of beta-blockers on aortic dilation with our current data (since most of our patients did not have serial CT scans), and this study has shown that the proportion of patients with Marfan syndrome on beta-blockade medication is surprisingly very low. In addition, we are unaware of routine standardized echo assessment of the aortic

root diameter in these patients to monitor progression. Despite the advances in surgical and medical therapy, namely, the Bentall operation and beta-blockers, the mortality in patients with Marfan syndrome remains high, with a mean age at death of 41.0 years (range 0-83) for males and 29.9 years (range 0-59) for females.

In this study, the majority of patients died of cardiovascular causes or sudden collapse, but there is no standardized medical program offered to patients with Marfan syndrome or their families to prevent such mortalities. Because of the relatively small number of patients in this study population who had successful treatment of aortic dissection, one cannot conclude that surgical repair confers a mortality advantage, although we have shown that aortoiliac disease in patients with Marfan syndrome is associated with a worse prognosis. A previous study by Krause[17] showed that prophylactic screening of patients with Marfan syndrome for aortic root dilation and cardiovascular disease is important in order to prevent mortality as emergency surgery and history of aortic complications in first-degree relatives are associated with a poorer prognosis.

We hope that physicians are more aware of the diagnosis of patients with Marfan syndrome. With a standardized clinical assessment and treatment protocol with risk factor management (mainly with beta-blockers), periodical echo assessment of the aortic root diameter progression, and gene mutation analysis, early mortality in this group of patients can be prevented.

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