SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2572.

KOLONICS-FARKAS ABIGÉL MARGIT

Légzőszervi megbetegedések
című program

Programvezető: Dr. Losonczy György, egyetemi tanár

Témavezető: Dr. Müller Veronika, egyetemi tanár

PULMONARY ASSESSMENT OF PATIENTS WITH MARFAN SYNDROME

Doctoral Thesis

Abigél Margit Kolonics-Farkas M.D.

Doctoral School of Károly Rácz Clinical Medicine

Semmelweis University

Supervisor:	Veronika Müller D.Sc.
Official reviewers:	Szilvia Soós Ph.D. Dóra Haluszka Ph.D.
Head of the Complex Examination Committee:	Zoltán Benyó D.Sc.
Members of the Complex Exam Committee:	Dóra Krikovszky Ph.D. János Varga Ph.D.

Budapest
2021

Table of Contents

1. Abbreviations

ACE: angiotensin-converting enzyme
ACTA: actin alpha
ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs
ADAMTSL: ADAMTS-like protein
AP: anteroposterior
ATS: American Thoracic Society
BB: beta-blocker
CAT®: COPD Assessment Test
CBS: cystathionine beta-synthase
cDNA: complementary DNA
COL1A2: collagen type I alpha 2 chain
COL3A1: collagen type III alpha 1 chain
COPD: chronic obstructive pulmonary disease
CT: computed tomography
dHPLC: denaturing high-performance liquid chromatography
DLCO: diffusing capacity of the lung for carbon monoxide
ECCS: European Community of Coal and Steel
EDS: Ehlers-Danlos syndrome
EGF: epidermal growth factor
FBN1: fibrillin-1 gene
FBN*:* fibrillin glycoprotein
FBN-1: fibrillin-1 glycoprotein
FBN-2: fibrillin-2 glycoprotein
FBN-3: fibrillin 3 glycoprotein
FEF25-75: forced expiratory flow between 25 and 75% of FVC
FEV1: forced expiratory volume in 1 second
FRC: functional residual capacity
FTAA: familial thoracic aortic aneurysm syndrome
FVC: forced vital capacity
GLI: Global Lung Functiosn Initiative
HR: heart rate
HRM: high resolution melting analysis
IVC: inspiratory vital capacity
KCNJ: potassium inwardly rectifying channel subfamily J
KLCO: diffusing capacity for carbon monoxide
LF: lung function
LDS: Loeys-Dietz syndrome
LLN: lower limit of normal
Mf: patients with Marfan syndrome without thoracic surgery
Mf_{op}: patients with Marfan syndrome who underwent major thoracic surgery
MFS: Marfan syndrome
mMRC: modified Medical Research Council
MTS: major thoracic surgery
MYH: myosin heavy chain
NOTCH1: Notch homolog 1, translocation-associated

PEF: peak expiratory flow

PLOD1: procollagen-lysine,2-oxoglutarate 5-dioxygenase 1

PTX: pneumothorax

RV: residual volume

SCAPIS: Swedish CArdioPulmonary bioImage Study

SEM: standard error of the mean

SLC2A10: solute carrier family 2 member 10

SpO2: blood oxygen saturation level

SSCP: single strand conformation polymorphism

TGF-β: transforming growth factor beta

TGFBR: transforming growth factor beta receptor

TLC: total lung capacity

TLCO: transfer factor of the lung for carbon monoxide

TRV: transversalis

US/LS: upper segment/lower segment ratio

VAS: Visual Analogue Scale

VC: vital capacity

6MWT: 6-minute walk test

2. Introduction

2.1. Definition, molecular and genetic properties

Marfan syndrome (MFS) is a systemic connective tissue disorder, which predominantly affects the skeletal, ocular and cardiovascular systems, but pulmonary manifestations are also common. While most affected patients inherit the disease in an autosomal dominant fashion, up to one-fourth of cases occur as a result of *de novo* mutations [1]. The disorder was first described by the French paediatrician, Antoine Marfan, in 1896. He reported the case of a 5-year old girl, Gabrielle, who had long, slender digits and other skeletal abnormalities [2]. In 1991, the underlying changes of the glycoprotein fibrillin-1 (FBN-1), encoded by the *fibrillin-1 gene* (*FBN1*) was established, which is located in chromosome 15 at position 15q21.1 [3, 4]. A total of 3077 mutations in the affected gene are currently known, of which more than 1300 lead to MFS [5].

Fibrillin (FBN) is a large glycoprotein which can be isolated from fibroblast cell cultures and is a component of microfibrils that can be found everywhere in the connective tissue. The FBN molecule was first cloned using a human placental complementary DNA (cDNA) library from a pool of mixed oligonucleotides that included all FBN peptide sequence options [6]. The amino acid sequence derived from the cDNA library revealed a modular domain structure with primarily epidermal growth factor-like (EGF) and 8-cysteine containing domains [7].

FBNs are large (~350 kDa) structural macromolecules, they contribute to the integrity and function of all connective tissues. They are considered to be structural macromolecules, because, like collagens, the FBNs form fibers that are visible in transmission electron micrographs. Unlike collagens, FBNs form microfibrils with uniform diameters (10-12 nm) that are not periodically cross-striated or “banded”. Fibrillin microfibrils display a typical morphology consisting of light and dark or hollow areas that give the appearance of railroad tracks (Figure 1.) [8, 9].

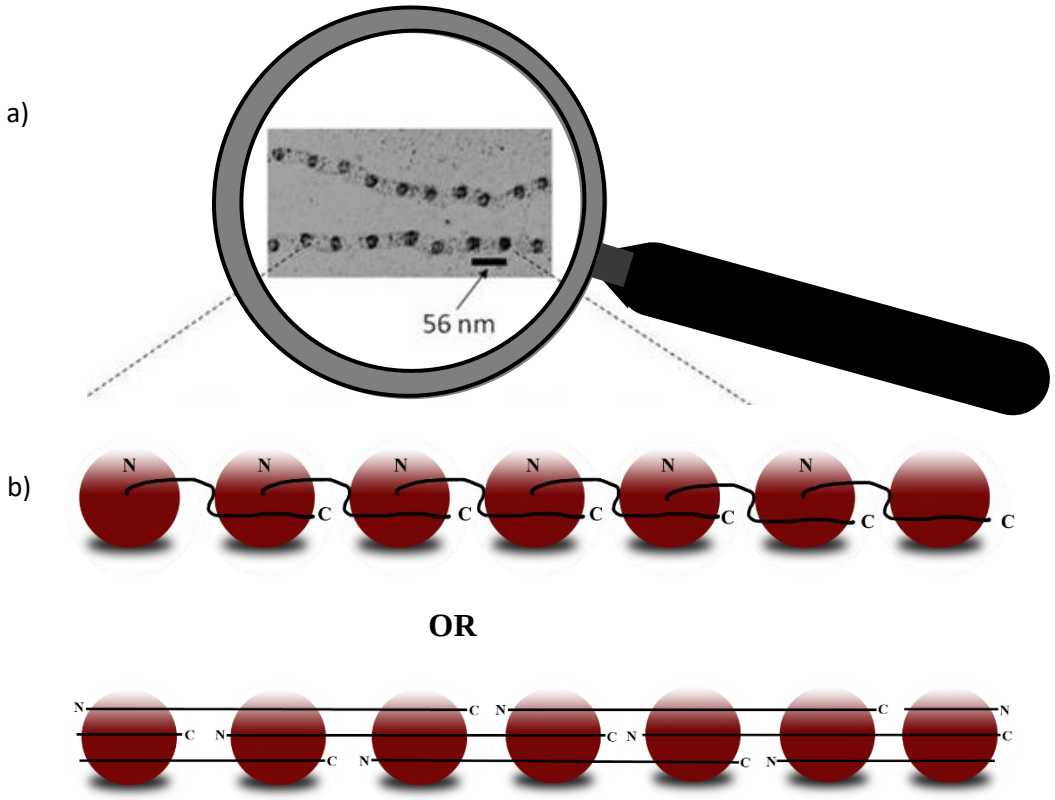


Figure 1. a) Electron microscopy image of isolated microfibrils; b) The two main models currently proposed to explain the organisation of fibrillin within the microfibrils: a folded back or extended structure. (Figure based on the work of [9].)

Microfibrils have a wide array of functions including the maintenance of elastic fibers and anchoring epithelial cells to the interstitial matrix [10, 11]. They exist as large bundles of short individual microfibrils (usually in close proximity to basal membranes, for example on the endothelial cell side of the glomerular basement membrane), or as the peripheral microfibril mantle around elastin in all elastic fibers [8]. The FBN network forms a frame into which the elastin is deposited, creating elastic fibers [12]. Dynamic connective tissues are created that can be stretched to a high degree while retaining their elasticity [13]. If error occurs in the process of FBN synthesis, among others it causes abnormality in the elasticity of the skeletal system and large vessels [14].

In the different types of connective tissue, fibrillin microfibrils are organized to best fit to the function of the tissue: e.g., in skin, elastic fibers form a loose network of interconnecting highways; in the dermis, the highways run parallel to the epidermis with

turn-offs coursing perpendicularly up from the deeper elastic fibers to the basal membrane at the dermal-epidermal junction, where bundles of microfibrils cross the lamina densa. In tendons and perichondrium/periosteum, elastic fibers run parallel to the long axis; in muscular arteries they infold the lumen [8].

So far, 3 different genes encoding FBN have been described in humans [15]. In MFS, the affected gene is *FBN1*, which is responsible for the production of FBN-1 matrix protein. *FBN1* contains 65 exons and it is estimated to be 110 kilobases long [16]. The FBN-1 protein consists of 2871 amino acids and has a repetitive structure of functional motives [17]. Mutations in the *FBN1* gene have been shown to cause a wide spectrum of microfibrilopathies, called 'type-1 fibrillinopathies', varying from isolated skeletal characteristics of MFS or familial ectopia lentis to neonatal MFS [18]. Most abnormalities associated with the syndrome can be explained by the structural malfunction of the connective tissue. Based on the results of experiments in mouse models of MFS, an increased production of transforming growth factor β (TGF- β) is most likely in the presence of insufficient production of FBN-1. TGF-β indirectly regulates connective tissue formation and structure development. This hypothesis is also supported by the fact that TGF-β type II receptor mutations cause similar symptoms to MFS called Loeys-Dietz syndrome (LDS) [19]. Habashi et al. demonstrated that aortic aneurysm in a mouse model of MFS is associated with increased TGF- β signalling [20].

In addition to *FBN1*, the slightly different *FBN2* and *FBN3* are all related to the formation and maintenance of the extracellular matrix (ECM) [21]. The *FBN2* gene is located at the 5q23.3 gene locus on chromosome 5 [22]. The product of *FBN2* is the FBN-2 protein, which is closely related to FBN-1. The domain structure, as well as the number and sequence of motifs, are the same in the two proteins. Domains B and D of FBN-1 and FBN-2 are 80% identical at the amino acid level. However, FBN-1 and FBN-2 also have important differences, which may reflect to differing functional roles [23]. The mutations of *FBN2* lead to Beals-Hecht syndrome phenotype [24]. *FBN3* is located at the 19p13.2 gene locus on chromosome 19. The gene is most highly expressed in foetal tissues and its protein product is localized to extracellular microfibrils of developing skeletal elements, skin, lung, kidney, and skeletal muscle. This gene is potentially involved in Weill-Marchesani syndrome [25].

2.2. Pathophysiology, epidemiology and clinical characteristics of MFS

2.2.1. Pathophysiology

Despite the progress that has been made in understanding MFS and other similar genetic diseases in the last few decades, the exact molecular mechanism leading to the development of different phenotypes is still not clearly understood [26]. At this time, abnormal homeostasis of the ECM is thought to be the underlying cause of the various manifestation of MFS. The reduced production or the malfunctioning FBN-1 lead to altered mechanical properties in the tissues, increased TGF-β activity and loss of cell-matrix interactions [27]. Heterozygous patients are also known to have clinical symptoms, which confirms the conclusion that many *FBN1* mutations are expected to exert a dominant negative effect, whereby mutant FBN-monomers impair the global function of the microfibrils [23]. Homozygous and compound heterozygous cases are rare and have been associated with severe clinical presentation [28].

MFS patients develop extensive lesions in the tunica media of the aorta, such as fragmentation, disorganization, and a progressive, subsequent remodelling of the lamina elastica with the incorporation of glycosaminoglycans. In this layer areas with smaller cell counts are formed. Accordingly, this lesion observed under the microscope was previously also called “cystic media necrosis”. The term " cystic media necrosis " is sometimes replaced by "cystic medial degeneration", as necrosis is not always present in the pathologic process and the latter can be the underlying factor responsible for a rupture of the vasa vasorum [29–31]. This type of microscopic structural degeneration is considered by some to be pathognomonic for MFS, however, it is not specific to the disease; it can be observed in all thoracic aortic dissections [27]. The abnormal homeostasis is thought to result in vascular remodelling, characterized by an exaggerated elastolysis as a result of overexpression of matrix metalloproteinases (matrix metalloproteinases 2 and 9), and increased hyaluronan content [32, 33].

2.2.2. Epidemiology

The prevalence of MFS is between 1.5-10.2/100000 [34, 35]. Based on these data, there are approximately 1000 MFS patients in Hungary. The incidence of the disease is ~0.2/100000; accordingly there may be 20 newly diagnosed cases in Hungary per year. [36]. There is no apparent enrichment in any ethnic or racial group and no sex preference was observed [37].

2.2.3. Clinical characteristics

Due to the molecular and histopathological characteristics of MFS, it leads to systemic connective tissue weakness with diverse symptoms. In contrast, some patients may be asymptomatic [38].
In the following sections the most common organ abnormalities and symptoms caused by the disease are summarized.

2.2.3.1. Musculoskeletal system

Disproportionate, excessive long-bone overgrowth (dolichostenomelia, Figure 2.) is one of the most common symptom of MFS [1]. Normally, a person's arm span should be less than their body height; an increased arm span to body height ratio of >1.05 is considered as a positive sign for MFS.[39, 40]. Reduced upper segment/lower segment ratio (US/LS or trunk vs. legs ratio) is also typical. This ratio is the value obtained by dividing the upper body segment (total height minus sthe lower segment) by the lower segment. Lower body segment is the measured distance from pubic bone to the floor in a standing position [41, 42]. However, this ratio can only be interpreted if there is no pronounced scoliosis (>20°) [1, 43]. Still, scoliosis is present in 45-70% of the cases, which makes the US/LS calculation uneasy in MFS patients (Figure 2., panel C/3) [44, 45]. Chest deformities caused by the overgrowth of the ribs are common and push the ribs forwards or backwards. Therefore, pectus carinatum (pigeon chest), pectus excavatum (funnel chest) or chest asymmetry are frequent skeletal abnormalities in MFS. Arachnodactyly (overgrowth of the fingers) is mostly a subjective finding. The combination of long fingers and loose joints results in the Walker-Murdoch or wrist sign: full overlap of the

distal phalanges of the thumb and fifth finger when wrapped around the contralateral wrist (Figure 2., panel B/1,2). The Steinberg or thumb sign is present when the distal phalanx of the thumb fully extends beyond the ulnar border of the hand when bended through the palm (Figure 2, panel B/3) [1, 46].

Acetabular protrusion also occurs in MFS, and it might be asymptomatic in young patients until hip osteoarthritis develops, but it can also lead to mild or moderate pain and restricted range of motions [47, 48]. Flat fleet are frequently present and vary from asymptomatic to severe form, in which the medial displacement of the medial malleolus results in the loss of the medial longitudinal arch with reactive hip and knee disturbances [1, 49]. While joint laxity and hypermobility can be often identified, in some cases joints show no abnormality or even contractures occur. Reduced elbow extension (when the angle between the upper and lower arm measures 170° or less upon full extension) indicates major involvement of the musculoskeletal system [50]. Camptodactyly is a frequent feature in the syndrome, particularly in children with severe and rapidly progressive MFS. Craniofacial deformities are also often present, including long, narrow skull (dolicocephaly), high-arched palate, tooth crowding, recessed lower mandible (retrognathia), small chin (micrognathia), malar flattening, and downward-slanting palpebral fissures [1].

2.2.3.2. Ocular system

In ~60% of MFS patients subluxation or even dislocation of the lens and subsequent ectopia lentis develops due to the weakness of the ciliary zonules [51, 52]. However, it should be emphasized, that this abnormality is not specific for MFS; it may also occur in homocystinuria, Weill-Marchesani syndrome and familial ectopia lentis [53]. Other ocular manifestations include severe, early-onset myopia, flat cornea, increased axial length of the eye, iris and ciliary muscle hypoplasia [54]. Literature data confirm that in MFS the lens is significantly thicker compared to healthy population [55]. Retinal detachment, early cataract development and glaucoma may also occur [53]. Surgical correction of ocular manifestations due to the special anatomy of the eye is therefore a serious challenge [56].

2.2.3.3. Cardiovascular system

The cardiovascular manifestations of the syndrome were first described by Victor A. McKusick in 1955 [57]. Regarding heart abnormalities, the mitral valves are most commonly affected. Thickening of the valve leaflets is often associated with prolapse of the bicuspid and/or tricuspid valves with the possibility of consequent regurgitation [58, 59]. Calcification of the mitral annulus in individuals younger than 40 years may also occur [1]. Progressive aneurysmal dilatation due to the inherent weakness of the aortic wall may appear [60]. Higher incidence of supraventricular and ventricular arrhythmias can also be observed, which may be a consequence of valvular insufficiency [61]. Literature data suggest, that development of long QT syndrome should also be considered [62]. It has also emerged, that MFS patients are more likely to develop dilated cardiomyopathy than healthy people. The study of Alpendurada et al. supported the existence of primary cardiomyopathy in MFS, pointing out that not only secondary cardiomyopathy can develop in this disease [63]. Aortic root dilatation and aortic aneurism also occur frequently in patients with MFS (Figure 2, panel C/2.). The formation and progression of these anomalies are age-dependent, therefore it is necessary to monitor the heart regularly with ultrasound and other imaging methods, such as computed tomography (CT). The most serious complication of this condition is the dissection of the aorta, which, in severe cases, can develop in utero, while in other cases aortic dilation never reaches a size that needs surgical intervention. Dilation is most common on the aortic root, contrary to e.g. atherosclerotic aneurysm, which is mainly observed on the abdominal aorta. In some cases, the carotid arteries may also be involved, which can lead to neurological symptoms due to cerebrovascular insufficiency [1, 64]. Involvement of the coronary arteries may cause myocardial infarction or sudden cardiac arrest. The mechanism of death usually includes rupture into the pericardial sac with subsequent pericardial tamponade [1, 65, 66]. Additionally, the main pulmonary artery diameter was significantly larger in patients with MFS at all ages when compared with controls. In the adult group (≥14 years), a cut-off value of 23 mm is provided to define pulmonary artery dilatation [67].

2.2.3.4. Respiratory system

Several factors can lead to respiratory abnormalities in MFS, including pectus carinatum and pectus excavatum, scoliosis, aortic root and ascending aorta dilation (which can even change the respiratory mechanics), aortic dissection, spontaneous pneumothorax (PTX), and the presence of apical blebs and bullae (Figure 2., panel C/3.) [44, 68, 69]. Blebs and bullae affecting the distal airways play a role in the development of spontaneous PTX, which occurs in 4-15% of the cases [70, 71]. The previously mentioned pectus excavatum and progressive scoliosis may cause restrictive ventilatory defect [72]. Beside these restrictive respiratory changes – which occur not only because of chest and spinal deformities but also due to pulmonary fibrosis –, obstructive ventilatory pattern can also be observed, caused by emphysema, airway collapse and sleep apnoea due to the abnormal structure of FBN-1. The latter is due to upper respiratory tract involvement and craniofacial lesions [73]. Therefore, it is of paramount importance to understand the changes affecting the lungs and to study their effects on clinical outcome.

In a study of Corsico et al., only 37% of patients with MFS had normal lung function (LF), while 19% showed a restrictive and 44% an obstructive pattern or an isolated diffusion impairment or an isolated hyperinflation. All patients with PTX showed an obstructive pattern and diffusion impairment [74]. These observations were also confirmed by a study published by our working group [75]. Decreased carbon monoxide diffusion capacity (DLCO) was also confirmed by observations from other centres [76, 77]. Lung abnormalities are evident in the immediate postnatal period and manifest as a developmental impairment of distal alveolar septation [78, 79].

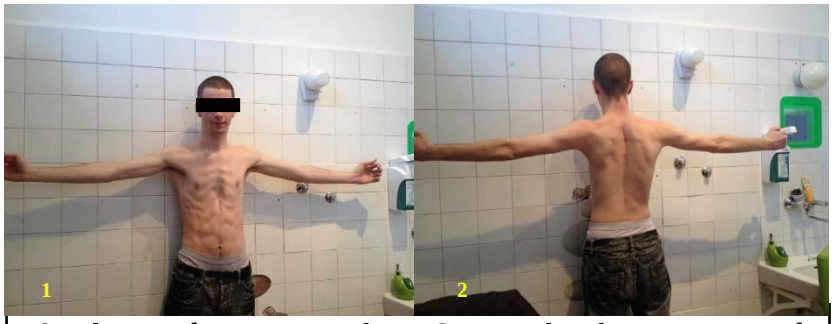
2.2.3.5. Skin and integument

The most common manifestations of the skin are striae atrophicae, which occurs in about two- thirds of patients [70, 80]. Important cutaneous features of MFS are striae distensae, a finding shared with LDS. However, Marfan patients typically have a normal texture and elasticity of the skin in contrast to LDS and Ehlers-Danlos syndrome (EDS) [81]. Unusual atrophic patches can be alarming symptoms of the disease [82].

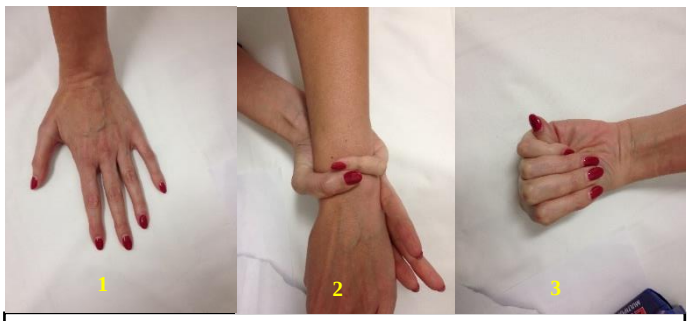
These stretch marks differ from those without connective tissue disorder, as that they cannot be linked to obesity, rapid muscle mass gain, or pregnancy. Another manifestation associated with connective tissue and skin weakness is inguinal hernia, which is often recurrent and may occur at birth or later in adults [83].

2.2.3.6. Nervous system

Dural ectasia is widening of the dural sac, and is often observable in patients with MFS [84]. It appears in 63-92% of the patients. The most common symptoms are lower back pain, weakness, headache, numbness above and below the affected limb; however, in most patients it is usually asymptomatic [85]. In this case, lumbosacral CT scan or magnetic resonance imaging can confirm its existence [86, 87]. Sacral meningocele with associated thinning of the sacral cortex, radiculopathy, constipation, urinary obstruction and postural headaches are common symptoms associated with this abnormality [84, 88–91].

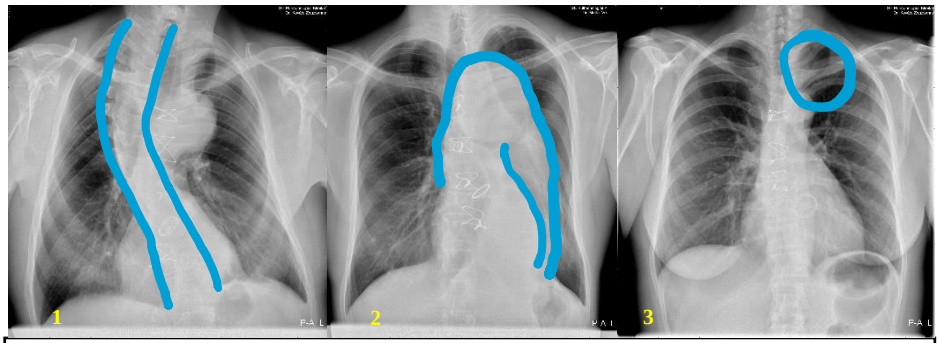


A: Photos of a patient with MFS. Note the characteristics of the disease: dolichostenomelia and pectus excavatum (1). Note the scar after surgical correction of the spine (2). (*Semmelweis University, Department of Pulmonology.)*



B: Arachnodactyly (1), wrist sign (2) and thumb sign (3) of a MFS patient. (*Semmelweis University, Department of Pulmonology.)*

Physical characteristics of MFS



C: X-ray image of scoliosis (1), aorta dilation (2) and apical bulla (3) of a MFS patient. Note the sternal sutures after major thoracic surgery. (*Semmelweis University, Department of Pulmonology.)*

Figure 2. Typical physical and radiological abnormalities in MFS.

2.3. Clinical diagnosis of MFS

The diagnosis for MFS has evolved recently, as various clinical expressions of the disease have been identified [92]. The Ghent nosology is applied worldwide to diagnose MFS. New molecular techniques allow the detection of FBN1 mutations in ~97% of MFS patients who fulfil the Ghent criteria [93, 94]. The genetic screening can be performed by using direct (e.g. Sanger sequencing) or indirect sequencing methods [94]. Indirect sequencing procedures include single strand conformation polymorphism (SSCP), denaturing high-performance liquid chromatography (dHPLC), heteroduplex analysis and high resolution melting analysis (HRM) [93, 95, 96].

2.3.1. Ghent nosology

To ease the diagnostic procedure, the clinical features of the syndrome were incorporated into a unified nosology at the University of Ghent, which has since been the foundation for establishing the diagnosis (Ghent nosology, 1996). The nosology consists of major and minor criteria. Major criteria include skeletal, cardiovascular and ocular symptoms. The co-existence of 2 major or 1 major and 2 minor criteria confirm the diagnosis (Table 1.) [97].

Table 1. The Ghent nosology (1996) [97].

Organ system (involvement)	**Major criteria**	**Minor criteria**
Skeletal	pectus carinatum	pectus excavatum of moderate severity
	pectus excavatum requiring surgery	
	reduced upper to lower segment ratio OR arm span to height ratio >1.05	joint hypermobility
	wrist and thumb signs	
	scoliosis of >20° or spondylolisthesis	high arched palate with crowding of teeth

Table 1. (Continued)

Organ system (involvement)	Major criteria	Minor criteria
	reduced extension at the elbows (<170°)	facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down- slanting palpebral fissures)
	medial displacement of the medial malleolus causing pes planus	
	protrusio acetabuli of any degree	
Cardiovascular	dilatation of the ascending aorta, with or without aortic regurgitation, and involving at least the sinuses of Valsalva dissection of the ascending aorta	mitral valve prolapse with or without mitral valve regurgitation
		dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonary stenosis or any other obvious cause (age<40 years)
		calcification of the mitral annulus (age<40 years)
		dilatation or dissection of the descending thoracic or abdominal aorta younger (age<50 years)
Pulmonary	-	spontaneous pneumothorax
		apical blebs
Ocular	ectopia lentis	flat cornea
		increased axial length of globe
		hypoplastic iris
		hypoplastic m. ciliaris

Table 1. (Continued)

Organ system (involvement)	Major criteria	Minor criteria
Skin and integument	-	striae atrophicae (stretch marks) without marked weight gain, pregnancy, or repetitive stress
		recurrent or incisional herniae
Dura	Lumbosacral dural ectasia	-
Family/genetic history	having a parent, child, or sibling who meets these diagnostic criteria independently	-
	presence of a mutation in *FBN1*, which is known to cause Marfan's syndrome	
	presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed Marfan's syndrome in the family	

Abbreviations: *FBN1*: fibrillin-1 gene.

A revised Ghent nosology was published in 2010, which brought changes in the diagnosis of MFS by abolishing the distinction of major and minor criteria, puts more weight on the cardiovascular manifestations of the disorder and sets aortic root aneurysm and ectopia lentis as cardinal features. emphasising the role of results of genetic tests, and introducing a score system for the classification of skeletal and other systemic symptoms [98, 99].

2.4. Differential diagnosis

The diverse manifestations of the syndrome overlap with numerous disorders; thus, the diagnosis of the syndrome is a complex task. The most important differential diagnostic diseases are summarized in Table 2. [98].

Table 2. Differential diagnosis of MFS [98].

Differential diagnosis	Affected gene(s)	Specific features
LDS	*TGFBR1* *TGFBR2*	Bifid uvula/cleft palate, arterial tortuosity, hypertelorism, diffuse aortic and arterial aneurysms, craniosynostosis, clubfoot, cervical spine instability, thin and velvety skin, easy bruising
Sphrintzen-Goldberg syndrome	*FBN1* and other	Craniosynostosis, mental retardation
Congenital contractural arachnodactyly	*FBN2*	Crumpled ears, contractures
Weill-Marchesani syndrome	*FBN1* *ADAMTS10*	Microspherophakia, brachydactyly, joint stiffness
Ectopia lentis syndrome	*FBN1* *LTBP2* *ADAMTSL4*	Lack of aortic root dilatation
Homocystinuria	*CBS*	Thrombosis, mental retardation
Familial thoracic aortic aneurysm syndrome (FTAA)	*TGFBR1* *TGFBR2* *ACTA2*	Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi
FTAA with bicuspid aortic valve	*NOTCH1* *KCNJ2* other	Aortic valve calcification, other congenital cardiac valve abnormalities

Table 2. (Continued)

Differential diagnosis	Affected gene(s)	Specific features
FTAA with patent ductus arteriosus	*MYH11*	Aortic aneurism, patent ductus arteriosus
Arterial tortuosity syndrome	*SLC2A10*	Generalised arterial tortuosity, arterial stenosis, facial dysmorphism
Ehlers-Danlos syndromes (vascular, valvular, kyphoscoliotic type)	*COL3A1* *COL1A2* *PLOD1*	Middle sized artery aneurysm, severe valvular insufficiency, translucent skin, dystrophic scars, facial characteristics

Abbreviations: FTAA: familial thoracic aortic aneurysm syndrome; TGFBR: transforming growth factor beta receptor; *FBN1*, *FBN2*: fibrillin-1 and 2 genes; ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; ADAMTSL: ADAMTS-like protein; CBS: cystathionine beta-synthase; ACTA: actin alpha; NOTCH1: Notch homolog 1, translocation-associated; KCNJ: potassium inwardly rectifying channel subfamily J; MYH: myosin heavy chain; SLC2A10: solute carrier family 2 member 10; COL3A1: collagen type III alpha 1 chain; COL1A2: collagen type I alpha 2 chain; PLOD1: procollagen-lysine,2-oxoglutarate 5-dioxygenase 1.

2.5. Therapeutic approaches in MFS

The general therapeutic approach of the syndrome is exercise reduction, pharmacotherapy, surgery, and, if necessary, endocarditis prophylaxis [100].

Due to the athletic, extremely tall stature and long limbs of MFS patients, many of them participate in athletic sports such as volleyball and basketball [101]. However, high levels of exercise, competitive athletics, and isometric exercise in particular increase the likelihood of aortic dissection, ocular problems, and skeletal complications [1]. Several guidelines have been made to optimize exercise levels in patients with the syndrome.

Most studies recommend avoiding isometric exercise altogether, such as lifting heavy weights, and prefer to perform moderate forms of aerobic exercise, such as running, swimming. Most patients, however, should be encouraged to remain active with aerobic

activities performed in moderation. This will promote skeletal, cardiovascular, and psychosocial health in the long term [38, 102].

Beta-blockers (BBs) are widely used to prevent or reduce the development of aortic aneurysms, which are common in MFS patients. This therapeutic approach was first proposed in 1971 by Halpern et al. [103]. The effect of BBs is based on the role of hemodynamic stress in the progressive enlargement of the proximal aorta. They also have negative inotropic and chronotropic effect, which is also beneficial in the syndrome [104]. Several retrospective studies have demonstrated the effectiveness of BBs in slowing aortic root growth [105–107].

Side effects of BBs are common and are much more pronounced in higher doses [108, 109]. Although with the use of cardioselective BBs higher tolerance can be achieved, some patients still do not tolerate any medications from this substance group. In these cases, a small number of clinical evidences support the efficacy of verapamil. This calcium channel blocker is intended to reduce the inotropy and chronotropy of the heart in these patients [105].

Another effective pharmaceutical therapy for pathological aortic root dilation is the use of angiotensin converting enzyme (ACE) inhibitors. They have been reported in the literature to increase aortic distensibility (dilatation) and reduce aortic stiffness [110].

Successful surgical treatment of the aortic root is perhaps the main reason for the significant increase in the life expectancy of MFS patients [111, 112]. In 1968, Bentall and DeBono revolutionized the cardiovascular surgery of aortic root dilation. The point of this type of surgery is that in case of aortic valve, aortic root and ascending aorta abnormality, they are replaced with a so-called „conduit", which is a 21-29 mm wide graft with inserted valve prosthesis [113]. Lifetime anticoagulant therapy is necessary in patients who have undergone valve replacement surgery [114]. In the last years a better understanding of benefits and risks of the various types of prostheses has resulted in a growing number of patients, even in a younger population, who prefer to choose a "biologic solution". There are several reasons for this trend. First, patients who receive biologic composite conduit (bio-Bentall) do not need lifelong anticoagulation therapy. Another important aspect is that the most recent prostheses available will last longer, as they are designed with new technologies and anti-calcification treatments. The valve-in-

valve approach using endovascular techniques may offer an effective, less invasive treatment for patients with valvular dysfunction of bioprostheses [115]. Finally, aortic valve-sparing interventions are established alternatives for patients with aortic root aneurysms, associated with reduced cardiac mortality and valve-related complications [116]. Elective surgery of the aortic root is performed when its maximum diameter exceeds 45 mm [117].

Individuals with MFS often have multiple abnormal cardiac valves. Abnormalities include myxomatous thickening with prolapse and regurgitation of the mitral and tricuspid valves, as well as dilatation of the aortic and pulmonary roots, with insufficiency of these valve leaflets. Accordingly, these individuals are at greater risk of bacterial endocarditis than those without structural heart disease. Antibiotic prophylaxis was recommended to diminish the likelihood of infective endocarditis in this setting [118].

2.6. Prognosis of MFS

Successful surgical treatment of the aortic root might be the main factor of the significantly increased life expectancy in MFS. As many organ systems are involved in the syndrome, the prognosis is highly variable. According to the publication of Murdoch et al. in 1972, the life expectancy of individuals with MFS is about two-thirds as compared to healthy people [119]. Data in 1995 suggested that life expectancy in MFS is nearly the same as in healthy population, and is increased in those who underwent aortic root surgery after 1980 [111]. As stated in a review article by Pyeritz in 2019, the life expectancy in MFS has essentially doubled over the past four decades [120]. The 5 and 10-year survival after the diagnosis is approximately 95% and 88%, and the five and 10 year complication free survival was 78% and 66%, respectively [121].

2.7. Pulmonary aspects of MFS - LF testing

The implementation of different examinations, tests and the use of already known and frequently used measurements are not challenging for those with average

anthropometrical parameters. At the same time, physicians may encounter cases, where the suitability of the measurement methods needs to be questioned.

2.7.1. LF testing in pulmonary diagnostics

LF testing is the basis of pulmonary diagnostics; its results must be accurate as they might have therapeutic consequences. Although most LF analysing methods are well established and widely employed, there are still many remaining questions regarding how tests should be performed, how to ensure reliable data, what reference values and rules should be used, and how LF testing should be interpreted to trustworthily support clinical decision making [122]. Even if the LF measurements are made in accordance with the highest technical requirements, their results can only be clinically valid if it is based on relevant and reliable reference values. There are more than 400 reference equations in the field of spirometry alone. Consequently, the default values set by the manufacturers are accepted regardless of whether they correspond to the ethnic or age group of the subject being studied [123]. Differences between equations origin from factors such as selection of healthy individuals, number of subjects involved, equipment, testing protocols, quality control, and statistical approach used to derive equations [124–127]. Consequently, the calculation of valid LF values in patients with above-average height poses challenges for clinicians: including 50% of the MFS patients who are above the 97th percentile including both sexes [128, 129].

2.7.1.1 Effect of age, sex, weight and height

LF reference values are traditionally based on anthropometric factors, such as height, sex, and age. Although weight is not a determining factor of lung size or function, body mass index (BMI) may influence LF results. [129].

In childhood until puberty, LF increases linearly in proportion to overall growth, which is at least partly determined by age and sex [130, 131]. The growth spurt in early adolescence is associated with the increased rate of general development and the rate of increase in static and dynamic LF parameters. Generally, girls achieve the maximum height and therefore the maximal lung volume earlier than boys [130]. There is a plateau

phase in LF between the ages of 20 and 30 years. However, some have a LF peak in their early 20s, while others, particularly men, may have the peak in their mid-30s [132].
In the general population the forced expiratory volume in 1 second (FEV1) decreases ~30 ml/year. Over the course of life, the total lung capacity (TLC) remains intact, as vital capacity (VC) decreases, while residual volume (RV) increases [133].

2.7.1.2 Effect of height and weight on LF

Taller persons have larger thoracic cage than shorter persons. Consequently, taller persons have larger lung volumes, higher maximal flow rates and higher DLCO. TLC, VC, RV, FVC and FEV1 are affected by height since they are proportional to body size. This means that a tall individual will experience greater decrease in lung volumes as they get older [129]. As an example, VC %predicted of a 40-year-old man who is 193 cm tall is 6 litres, while that of a man who is 163 cm tall is 4 litres. Therefore, the accurate measurement of standing height is very important in LF testing [129]. The use of alternative measures to determine height may cause errors in the predicted pulmonary function. There are many conditions and anthropometric features that might influence the LF results [133–135]. Height, BMI, hip circumference and body surface area are the strong determinants of pulmonary function [134]. Vertebral deformities are prevalent in chronic obstructive pulmonary disease (COPD) patients and may cause excessive loss of height. As height is used for calculating reference values in LF testing, larger than normal height reduction could cause overestimation of LF. As an example, the study of Kjensli et al. concluded that LF may be overestimated in a large proportion of COPD patients at relatively modest height [136]. Thus, the methodology of LF testing in patient populations with special anthropometric features should be questioned. The European Respiratory Society (ERS) advises to use arm span if the standing height of a patient cannot be measured due to certain conditions, e.g. kyphosis and kyphoscoliosis which appears often in MFS [137]. For the re-calculation of height from arm span in homogeneous Caucasian populations, the following equations are recommended by Parker et al.:
*Males: Height (m) = 68.74 + 0.63008·Arm span (m) − 0.1019*Age;*
Females: Height (m)=33.14+0.79499·Arm span (m) [138].

Body weight is much less important than standing height when predicting most LF values; as a result, weight should not be included into spirometric prediction equations. However, extremes in weight are associated with changes in lung volumes [139–142].

2.7.1.3 Reference equations in LF testing

The reference equations should be selected to best represent the characteristics of the patients tested. Reference equations should not be used in patients whose age or height is outside the range of subjects in the reference study [143].

In 1960 the European Community of Coal and Steel (ECCS) was the first organization to issue recommendations for spirometry and released equations for calculations of reference values [144, 145]. In Hungary the ECCS was used until recently, where height and age are major determinant of LF reference equations, and corrections are necessary for height in special patient populations. ECCS spirometry reference calculations are the following: *FVC men: 5.76H - 0.026A - 4.34; FVC women: 4.43H - 0.026A - 2.89 and FEV1 men: 4.30H - 0.029A - 2.49; FEV1 women: 3.95H - 0.025A - 2.69; (H—height in meters, A—age in years)* [75].

Large reference studies for spirometry have been performed in healthy subjects in Europe and in the United States [146–148]. These studies, the National Health and Nutrition Examination Survey and the Global Lung Function Initiative (GLI), have been used to generate reference equations for LF results [146], [123].

In 2012, the Global Lung Function Initiative (GLI) published spirometric prediction equations for ages between 3 and 95 years for ethnic and geographic groups in 26 countries comprising individuals of Caucasian, African American, North Asian, and Southeast Asian descent. These reference equations are endorsed by ERS, American Thoracic Society (ATS), American College of Chest Physicians, the Australian and New Zealand Society of Respiratory Science, Thoracic Society of Australia and New Zealand, and Asian Pacific Society for Respirology [143, 144, 149, 150]. The GLI equations apply a rigorous, age-appropriate methodology and are based on large sample populations that include older age groups and minority representation [148, 151].

2.7.1.4 Upper and lower limits of normality

Based on the recommendation if the ERS/ATS, the 5th percent is used as the lower limit of the normal range (LLN). This means, that 5% of healthy population have LF values below LLN [147]. For spirometry, LLN was calculated from reference equations that incorrectly assumed a linear relationship between predictor variables (age and height) and spirometric measures incorrectly assumed a normal distribution and constant variability for reference values [146, 152–155].

In the past, 80% of the predicted values were determined as LLN in most LF testing methodologies. Besides, even though no women had been tested, the ECCS issued reference values for females: using simply 80% of the values for males [144, 145]. This standard might work in case of defining FVC, FEV1, transfer factor of the lung for carbon monoxide (TLCO) and DLCO in middle-aged individuals, but in case of FEV1/FVC it gives false positive or false negative results especially when used for adolescents and adults over the age of 60 years [156]. The use of the LLN rather than a pre-set cut off (e.g. FEV1/FVC 0.7) to define airway obstruction reduces the misclassification that occurs by using a fixed ratio. The fixed ratio may neither be accurate in younger individuals (underdiagnosis) nor in older individuals (overdiagnosis) with airway obstruction. LLN incorporates the changes in FEV1/FVC that occur with age, hence decreases the chance for misclassification [157–161].

3. Objectives

As presented above, the interpretation of pleuropulmonary abnormalities and the identification of LF changes in patients with special anthropometric parameters can be challenging. In my doctoral thesis my aim was to detail the pulmonary assessment of patients in MFS, to determine the frequency of pulmonary symptoms and pleuropulmonary anomalies in this special patient population. I also examined the abnormalities in the patients' LF in the whole patient group and the individual LF changes using 2 different set of reference values.

In particular, the aim of my research was to assess the following:

1. Determination of pleuropulmonary abnormalities and their frequency in Hungarian MFS patients.

2. Investigation of LF abnormalities in MFS patients who have undergone major thoracic and/or spinal surgery (MTS) and in patients who did not need the procedure.

3. Recalculation of LF results with arm span corrected height ($H_{corrected}$) and the comparison of these results with the values calculated with the original measured standing height ($H_{measured}$).

4. Investigation of correlation between the patients' LF values and the extent of their scoliosis.

5. Comparison of LF results calculated with ECCS and GLI reference equations in the whole patient group and the analysis of the patients' own outcomes using ECCS and GLI reference equations.

6. Comparison of LF results in MFS patients: assessing better suitability of ECCS reference values by using $H_{corrected}$ or GLI calculated with $H_{measured}$.

4. Results

4.1 Determination of pleuropulmonary abnormalities and their frequency in Hungarian MFS patients

The study had a cross-sectional design. After a written inquiry, 55 Caucasian patients from the National Marfan Registry (established and supervised by the Hungarian Marfan Foundation) agreed to participate in the study [162]. All pulmonary examinations were voluntary. Exclusion criteria were age < 16 years and MTS within 6 months prior to the assessment. MTS was usually prophylactic aortic root surgery or intervention due to chest wall deformity and spine correction [163, 164]. Data on pleuropulmonary symptoms (dyspnoea, cough, sputum, chest pain), history of smoking, sex, age, standing height, bodyweight, BMI and arm span (cm) were collected. All patients have undergone earlobe arterialised capillary blood gas, chest X-ray and fluoroscopy, laboratory testing and electrocardiography. The 6-minute walk test (6MWT) was performed to measure exercise capacity according to ATS guidelines [165].

Patient characteristics are summarised in Table 3. The average age was 38.1± 13.1 years. Most patient had no history of smoking. The operated patients (Mf_{op}) have undergone MTS predominantly due to cardiac causes. Height correction resulted in significantly lower values in patients who did not need MTS procedure (Mf); however, this difference only appeared in men.

Table 3. Patient characteristics.

	All patients (n=55)	**Mf group (n=32)**	**Mf_{op} group (n=23)**	**p-value Mf vs. Mf_{op}**
Age (years)	38.1±13.1			
Men	32.6±11.6	32.4±11.0	33.9±11.1	n.s.
Women	40.8±13.2#	37.9±10.9	45.1±14.8	n.s.
Gender				
Men, n (%)	20 (36)	11 (34)	9 (39)	n.s.
Women, n (%)	35 (64)	21 (66)	14 (61)	n.s.
Weight (kg)	71.7±17.5			
Men	79.1±22.2	79.8±20.3	80.4±23.3	n.s.
Women	67.1±12.2	68.1±14.5	67.4±8.9	n.s.
Height (cm)				
a) Measured	182.3±10.0	183.1±8.5	181±11.8	n.s.
b) Corrected	179.5±7.4#	180.4±6.4#	177±8.4	n.s.
Men				
a) Measured	191.7±7.9	191.6±9.1	191.7±7.3	n.s.
b) Corrected	186.3±6.5	187.0±6.6#	185.2±6.6	n.s.
Women				
a. Measured	176.5±6.2	178.6±3.6	173.9±8.3	n.s.
b. Corrected	176.0±5.0	177.3±3.2	174.0±6.6	n.s.
BMI (kg/m^2)	21.5±4.5			
Men	21.5±5.7	21.1±4.7	23.0±6.2	n.s.
Women	21.5±3.7	21.1±4.4	22.3±2.8	n.s.
Arm span (cm)	185.1±9.3			
Men	191.8±10.2	193.0±10.2	190.3±9.9	n.s.
Women	181.7±6.8	183.3±4.4	179.1±8.7	n.s.
Smoking habit				
Never smoker, n (%)	40 (73)	25 (78)	15 (65)	n.s.
Former-smoker, n (%)	11 (20)	5 (16)	6 (26)	n.s.
Current smoker, n (%)	4 (7)	2 (6)	2 (9)	n.s.

Table 3. (Continued)

	All patients (n=55)	**Mf group (n=32)**	**Mf_{op} group (n=23)**	**p-value Mf vs. Mf_{op}**
Major thoracic surgery indication				
Cardiac, n (%)	19 (35)	0	19 (35)	Not analysed
Chest or spine deformity, n (%)	4 (7)	0	4 (7)	

Abbreviations: Mf: patients with Marfan syndrome without thoracic surgery; Mf_{op}: patients with Marfan syndrome who underwent major thoracic surgery; n.s.: not significant; BMI: body mass index.

significant difference compared to the value above

Thoracic deformities and respiratory symptoms are summarised in Table 4. Respiratory symptoms were present in >20% of the patients. Mf_{op} patients reported dyspnoea, cough and chest pain significantly more frequently compared to Mf group participants. Changes in lung structure confirmed by chest CT scans were rare. Scoliosis was significantly more frequent in the Mf_{op} as patients in the Mf group.

Table 4. Chest deformities and respiratory symptoms in patients with MFS.

	All patients (n=55)	**Mf group (n=32)**	**Mf_{op} group (n=23)**	**p-value Mf vs. Mf_{op}**
Chest deformities				
Pectus carinatum, n (%)	24 (48)	12 (38)	12 (52)	n.s.
Pectus excavatum, n (%)	14 (28)	6 (19)	6 (26)	n.s.
Scoliosis, n (%)	36 (72)	15 (47)	21 (91)	<0.01
Asymmetric chest, n (%)	19 (38)	11 (34)	8 (35)	n.s.
Structural abnormalities of the lung				
Spontaneous PTX, n (%)	5 (10)	3 (9)	2 (9)	n.s.
Apical blebs and bullae, n (%)	4 (8)	3 (9)	1 (4)	n.s.
Pleuropulmonary symptoms				
Cough, n (%)	11 (20)	5 (16)	6 (26)	<0.01
Sputum, n (%)	5 (9)	1 (3)	4 (17)	n.s.
Dyspnoea, n (%)	10 (18)	3 (9)	7 (30)	<0.01
Chest pain, n (%)	9 (16)	2 (6)	7 (30)	0.03

Abbreviations: Mf: patients with Marfan syndrome without thoracic surgery; Mf_{op}: patients with Marfan syndrome who underwent major thoracic surgery; PTX: pneumothorax; n.s.: not significant.

4.2 Investigation of LF abnormalities in Mf and in Mf_{op} patients

Evaluation of LF included measurements FVC, FEV1, FEV1/FVC, forced expiratory flow between 25 and 75% of FVC (FEF25–75), TLC, RV and functional residual capacity (FRC) by means of electronic spirometer and body plethysmography according to the ERS/ATS guidelines [166]. Three technically appropriate manoeuvres were performed and the highest value of them was used. TLCO and diffusing capacity for carbon monoxide (KLCO) were measured with single breath method. LF result are expressed as percentage of predicted values. We used the database of ECCS as baseline reference values, set by the spirometry manufacturer [167]. Reference equations using $H_{measured}$, may be inappropriate in MFS patients due to their special skeletal features, especially after thoracic surgery. In order to avoid any measurement bias or inaccuracy due to chest

and/or spine deformities, we used arm span to correct height ($H_{corrected}$) based on ERS recommendation [168]. We recalculated the LF values based on $H_{corrected}$ with the application of the original ECCS reference equations. The range of accuracy in the recommendations for forced expiratory manoeuvres FVC and FEV1 is±3% of reading or±0.050 L, depending on which one was the greater. The LF testing data using the ECCS reference and $H_{measured}$ are summarised in Table 5. Mf_{op} patients had significantly lower FVC, IVC (inspiratory vital capacity) and TLC as compared to Mf patients. Typically, IVC should be higher than FVC, but in 31 cases of the whole patient group we detected higher FVC than IVC values. Some investigators have reported slightly higher FVC than IVC in normal subjects and in patients with COPD [169, 170]. However, we cannot exclude that this phenomenon might be related to chest deformities which occur frequently in MFS. FEV1/FVC values were suggestive for an obstructive ventilatory pattern in Mf_{op} patients. Obstruction severity in Mf_{op}, expressed as %predicted FEV1, were in line with moderate changes. Airway obstruction in Mf_{op} patients was proved by significantly declined FEF25–75 values compared to Mf patients. Increased RV and FRC, both indicating hyperinflation, were observed in both groups. Diffusion (TLCO and KLCO), blood gas parameters, 6MWT data or quality of life did not differ between groups. The CAT® score is a patient-completed instrument to assess and quantify health-related quality of life and symptom burden in COPD patients. It comprises 8 questions, each is presented as a semantic 6-point (0-5) differential scale, providing a total score out of 40. Scores of 0-10, 11-20, 21-30, 31-40 represent mild, moderate, severe or very severe clinical impact, respectively [171–173]. The Medical Research Council (mMRC) dyspnoea score is a 5-point (0-4) scale based on the severity of dyspnoea [174]. CAT® and mMRC tests indicated elevated values in the Mf_{op} group with more respiratory symptoms. To assess general quality of life, the Visual Analogue Scale (VAS) was used. VAS is a 100-point numeric rating scale to measure the general condition of the patients. Zero point means the worst imaginable condition, while 100 points symbolises the best possible general condition [175]. According to the result of VAS, there was no significant difference between the Mf and Mf_{op} groups regarding their general condition. The results of quality of life measurements are summarized in Table 5.

Table 5. LF testing in Mf and Mf_{op} using $H_{measured}$ for the ECCS equations.

	All patients (n=55)	**Mf group (n=32)**	**Mf_{op} group (n=23)**	**p-value Mf vs. Mf_{op}**
FVC (L)	4.20±1.10	4.53±1.06	3.75±1.02	p=0.01
FVC (%)	93.38±17.54	97.55±15.66	86.48±18.05	p=0.02
FEV1 (L)	3.24±0.10	3.60±0.93	2.76±0.79	p<0.01
FEV1 (%)	84.13±18.52	91.06±17.02	75.06±16.69	p<0.01
FEF25-75 (L/s)	2.96±1.24	3.40±1.20	2.35±0.99	p<0.01
FEF25-75 (%)	71.49±29.50	80.32±31.16	59.40±21.18	p=0.01
PEF (L/s)	6.25±1.72	6.56±1.63	5.90±1.81	n.s.
PEF (%)	74.25±18.08	77.39±18.77	70.99±16.79	n.s.
RV (%)	125.86±30.42	128.45±34.67	124.03±27.01	n.s.
FRC (%)	122.70±26.42	120.85±27.66	124.03±25.45	n.s.
TLC (L)	5.90±1.26	6.27±1.20	5.41±1.20	p=0.01
TLC (%)	87.83±14.51	92.97±11.41	82.57±16.33	p<0.01
IVC (L)	4.16±1.08	4.43±1.06	3.80 ± 1.03	p=0.03
IVC (%)	87.25±16.82	91.27±15.29	82.72±17.82	p=0.05
FEV1/FVC	0.77±0.10	0.80±0.11	0.74±0.08	p=0.03
FEV1/IVC	0.80±0.16	0.82±0.12	0.71±0.18	p<0.01
TLCO (mmol/min/kPa)	10.01±2.83	10.74±2.82	9.24±2.68	n.s.
TLCO (%)	89.55±18.43	94.64±17.97	85.17±18.02	n.s.
KLCO [mmol/min/kPa/L]	1.72±0.32	1.77±0.30	1.68±0.34	n.s.
KLCO (%)	80.57±17.11	80.69±19.00	81.50±14.68	n.s.
Blood gases				
pH	7.42±0.02	7.41±0.02	7.42±0.01	n.s.
pO_2 (mmHg)	83.28±7.02	83.88±6.24	82.41±8.09	n.s.
pCO_2 (mmHg)	37.42±3.21	37.13±0.02	37.84±3.19	n.s.

Table 5. (Continued)

	All patients (n=55)	Mf group (n=32)	Mf_{op} group (n=23)	p-value Mf vs. Mf_{op}
6MWT				
Distance (m)	566.7±99.06	584.28±92.82	542.22±104.27	n.s.
ΔHR (1/min)	34.40±12.65	40.03±11.20	26.57±7.43	n.s.
ΔSpO2 (%)	1.02±8.36	1.53±2.4	0.30±1.36	n.s.
Quality of life				
VAS (1-100)	78.39±19.67	81.37±18.01	74.16±21.61	n.s.
CAT (0-40)§	7 (0-22)	7 (0-22)	10 (0-22)	n.s.
mMRC (0-4)§	0 (0-3)	0 (0-2)	1 (0-3)	n.s.

Abbreviations: Mf: patients with Marfan syndrome without thoracic surgery; Mf_{op}: patients with Marfan syndrome who underwent major thoracic surgery; n.s.: not significant; FVC: forced vital capacity; FEV1 forced expiratory volume in 1 second;:FEF25-75: forced expiratory flow between 25 and 75% of FVC; PEF: peak expiratory flow; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; IVC: inspiratory vital capacity; TLCO: transfer factor of the lung for carbon monoxide; KLCO: diffusing capacity for carbon monoxide; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; 6MWT: 6-minute walk test; ΔHR: heart rate change; ΔSpO2: blood oxygen saturation level change; VAS: Visual Analogue Scale; CAT®: COPD Assessment Test; mMRC: modified Medical Research Council.

§ data expressed as median (range)

4.3 Recalculation of LF results based on $H_{corrected}$

With the application of $H_{corrected}$, FVC and FEV1 %predicted values increased in every patient groups (Table 6.). FEV1% remained in the pathological range in Mf_{op} patients (<80% predicted) and remained significantly lower compared to Mf group.

Table 6. Lung function parameters using ECCS with $H_{measured}$ and $H_{corrected}$ in MFS patients.

		All patients (n=55)	**Mf group (n=32)**	**Mf_{op} group (n=23)**	**p-value Mf vs. Mf_{op}**
FVC%	ECCS $H_{measured}$	93.38±17.54	97.55±15.66	86.48±18.05	p=0.02
	ECCS $H_{corrected}$	96.68±18.09	101.99±15.18	88.02±19.15	p=0.01
FEV1%	ECCS $H_{measured}$	84.13±18.52	91.06±17.02	75.06±16.69	p<0.01
	ECCS $H_{corrected}$	86.41±23.49	93.27±16.68	77.25±18.92	p<0.01

Abbreviations: Mf: patients with Marfan syndrome without thoracic surgery; Mf_{op}: patients with Marfan syndrome who underwent major thoracic surgery; ECCS: European Community of Coal and Steel; GLI: Global Lung Function Initiative.

4.4 Correlation between the patients' LF values and the extent of scoliosis

Scoliosis is a common feature in MFS. In our patient group significantly more individuals suffered from scoliosis in the Mf_{op} group compared to Mf group. Significant negative correlation between the extent of scoliosis and FVC% (r= −0.414, [95% CI−0.617 to−0.159], p=0.0023) and FEV1% (r= −0.401, [95% CI−0.607 to−0.144], p=0.003) were noted. Likewise, FVC% after calculating with $H_{corrected}$ (r= −0.463, [95% CI−0.661 to−0.206], p<0.001) and FEV1% (r= −0.386, [95% CI−0.599 to−0.125], p=0.005) confirmed the association. The correlation between the LF parameters and scoliosis is presented in Figure 3.

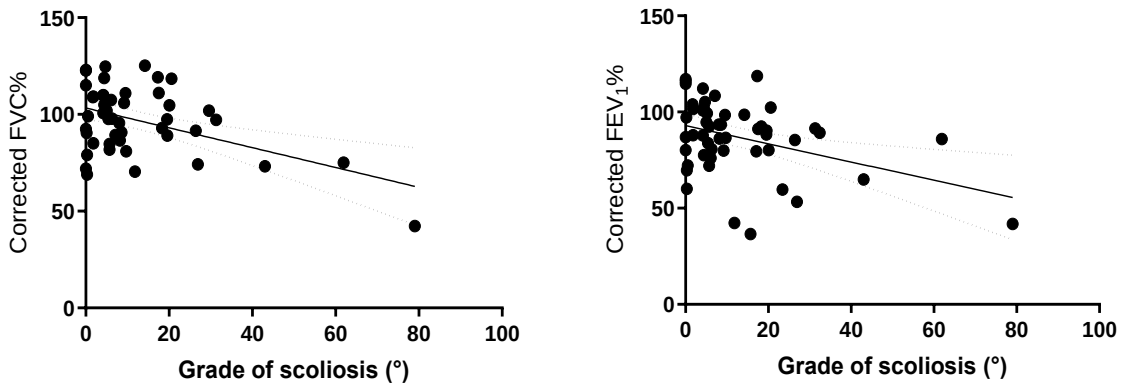


Figure 3. Correlation between the extent of scoliosis and $H_{corrected}$ FVC% (panel A) and FEV1% (panel B).

4.5 Comparison of LF results calculated with ECCS and GLI reference equations

In our further investigation from the pre-selected 55 patients, we chose individuals who did not have any coexistent pulmonary disease, did not use any pulmonary medications and had no acute respiratory symptoms (dyspnoea, cough, sputum and chest paint that was unusual in comparison to the chest complaints the patients had in the everyday life due to their chest deformities) during the assessment.

Investigation of LF parameters was performed in 32 asymptomatic adult MFS patient. We used the database of the ECCS set by the spirometry manufacturer as baseline reference values [167].

Recalculation of LF results with GLI equations was performed with the "GLI-2012 Desktop Software for Individual Calculations" software [176]. Mandatory data for the recalculation were sex, age, ethnicity, height, FVC and FEV1 values given in litres. Systemic score of the patients has been also evaluated (Table 7.). The systemic involvement can be confirmed when the score is ≥7 points [98, 177].

Table 7. Calculation of the systemic score in MFS [98].

Symptom	**Score**	**Number of affected patients, n (%)**
Wrist AND thumb sign	3	25 (78.1)
Wrist OR thumb sign	1	28 (87.5)
Pectus carinatum deformity	2	15 (46.9)
Pectus excavatum or chest asymmetry	1	14 (43.8)
Hindfoot deformity	2	5 (15.6)
Plain pes planus	1	14 (43.8)
Pneumothorax	2	2 (6.3)
Dural ectasia	2	2 (6.3)
Protrusio acetabuli	2	0 (0)
Reduced US/LS AND increased arm/height AND no severe scoliosis	1	8 (25.0)
Scoliosis or thoracolumbar kyphosis	1	25 (78.1)
Reduced elbow extension	1	8 (25.0)
Facial features (3/5) (dolichocephaly, enophtalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)	1	4 (12.5)
Skin striae	1	21 (65.6)
Myopia > 3 dioptres	1	21 (65.6)
Mitral valve prolapse (all types)	1	26 (81.2)

Abbreviations: US/LS: upper segment/lower segment ratio.

Clinical data and parameters of the patients are shown in Figure 4. Vast majority of the patients were never smokers. There were significantly more men in the ever smoker group as compared to women (p=0.02). Only 2 women had positive smoking history.

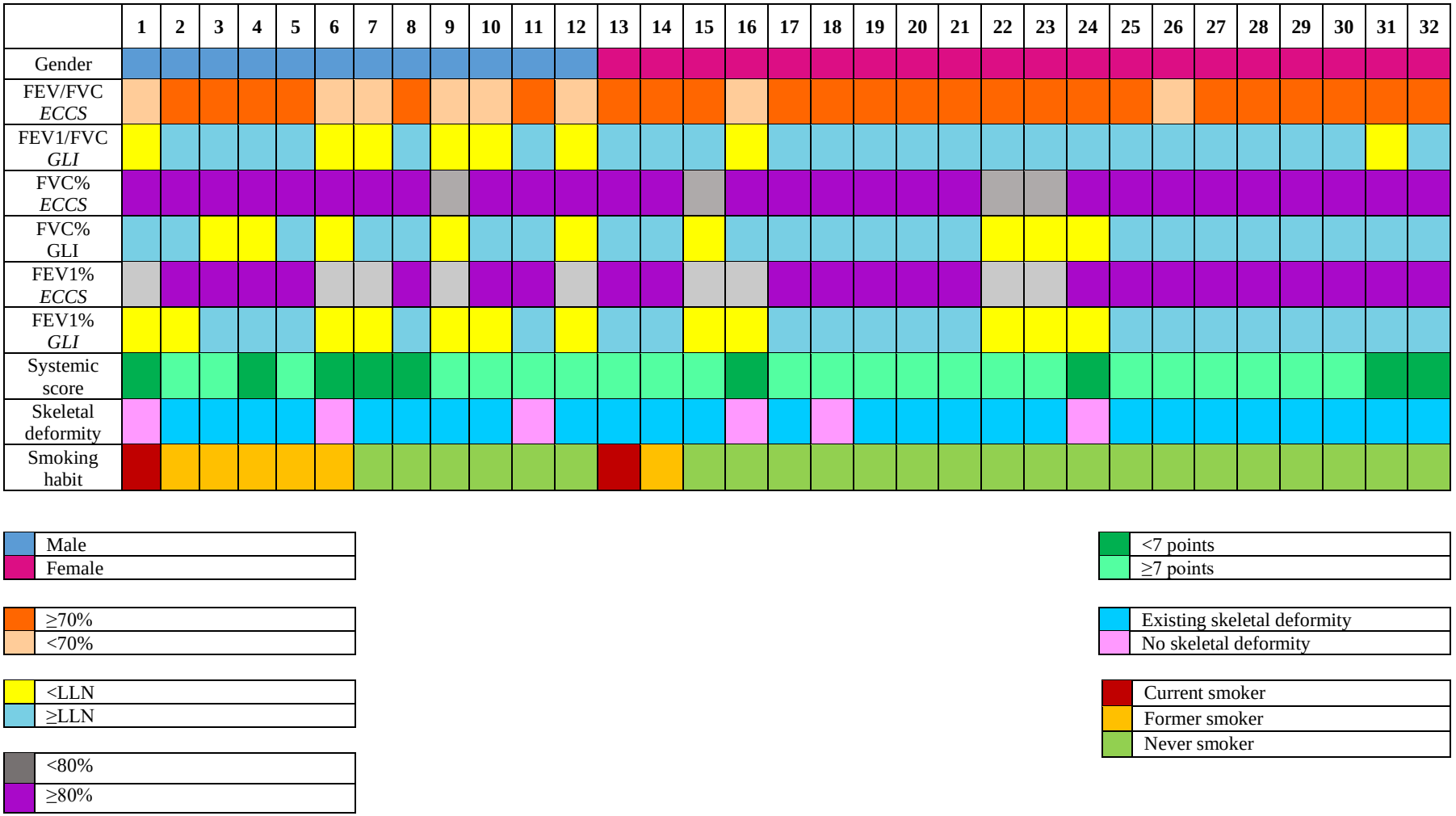


Figure 4. Graphic summary of individual clinical data.

LF results are summarized in Table 8. There were no significant differences between sexes regarding FVC% and FEV1% calculated with ECCS. Using GLI resulted in lower FVC% and FEV1% values, however the difference was not significant when compared with ECCS results. By using GLI LLN abnormal FVC% values could be observed twice as often as using ECCS. Airway obstruction appeared significantly more frequently with GLI LLN in men as compared to women. Obstruction severity expressed by FEV1% predicted (<80% reference or <LLN) was more pronounced in men using GLI equations.

Table 8. Lung function parameters using ECCS and GLI equations in MFS patients.

		All patients (n=32)	**Men (n=12)**	**Women (n=20)**	**p-value Men vs. Women**
FVC%	**ECCS**	97.1±16.9	93.4±12.4	99.3±19.0	n.s.
	GLI	87.0±16.6*	82.7±15.5*	89.4±17.1*	n.s.
	<LLN GLI, n (%)	9 (28)	5 (42)	4 (20)	n.s.
FEV1%	**ECCS**	88.0±19.1	83.4±17.9	90.7±18.1	n.s.
	GLI	79.6±18.9*	78.7±15.6§	80.2±21.2*	n.s.
	<LLN GLI, n (%)	11 (34)	6 (50)	5 (25)	n.s.
FEV1/FVC	**ECCS**	77.1±8.7	73.1±9.3	79.5±7.1	0.04
	GLI	71.0±2.7	70.2±2.4	71.5±2.8	n.s.
	<LLN GLI, n (%)	8 (25)	6 (50)	2 (10)	0.03

Abbreviations: FVC: forced vital capacity; FEV1 forced expiratory volume in 1 second; ECCS: European Community of Coal and Steel; GLI: Global Lung Function Initiative; LLN: lower limit of normal.

n.s.= not significant (p-value >0.05).

*=p-value<0.01 vs. ECCS, §= p-value=0.02 vs. ECCS.

There were also below threshold values regarding FEV1% (Figure 4., individual data). Patients were divided into 2 different groups based on their systemic scores: one group without (<7 points) and the other with systemic involvement (≥7 points). We compared FEV1/FVC using both ECCS and GLI in the 2 groups. In patients with systemic involvement the FEV1/FVC values were significantly lower when using GLI as compared to ECCS (Figure 5.).

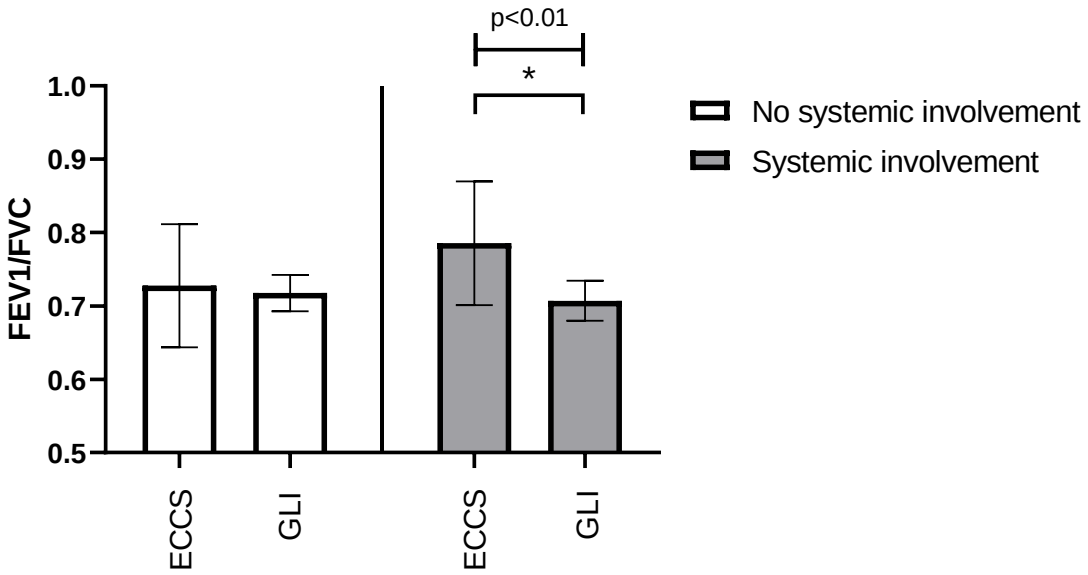


Figure 5. FEV1/FVC values calculated with ECCS and GLI in MFS patients with no systemic involvement and in MFS patients with systemic involvement.

Data were presented as mean ± standard deviation.

Relationship between the systemic score and FEV1/FVC values did not confirm association regardless of reference equation used ($p>0.05$ in all cases). However, GLI seemed to be more sensitive in showing obstructive ventilatory pattern in low systemic score patients (Figure 6).

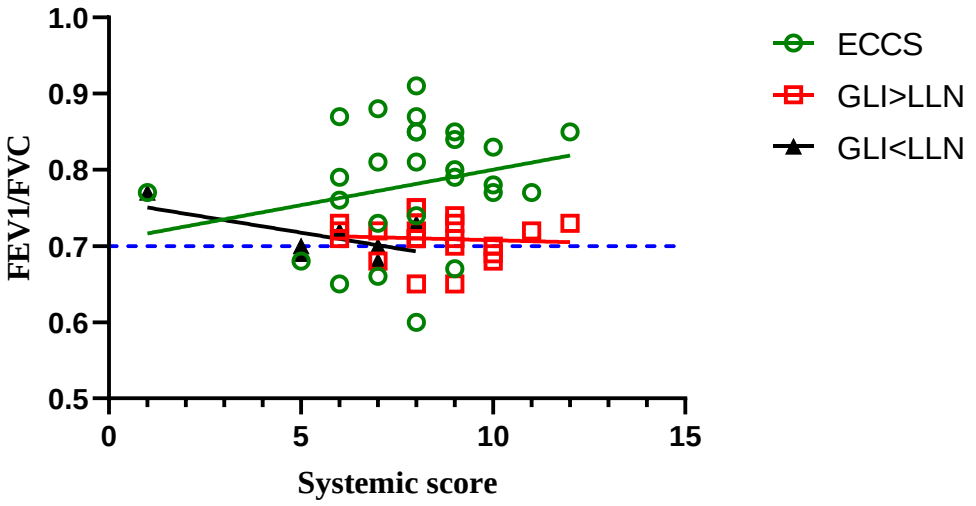


Figure 6. Association between MFS systemic score and FEV1/FVC when calculating with ECCS and GLI reference equations. The blue broken line marks the 70% of FEV1/FVC.

4.6 Comparison the conduciveness of height correction to arm span and GLI reference equations for LF measurements

In our first study about LF evaluation in MFS we used ECCS reference equations, which are routinely applied in Hungary. Yet we suspected that the measurements would be biased due to the disproportionate body height of the patients [128, 178]. After using $H_{corrected}$, higher LF % predicted results were obtained from the patients. However, since ECCS is already considered to be inaccurate in several large studies, in our later study we used GLI methodology, which is recently recommended in the international literature [179]. Its application confirmed obstructive and restrictive tendency both with or without height correction in our MFS patients, which is consistent with the disease characteristics (Figure 7.). FVC% estimated with ECCS $H_{measured}$ was significantly higher when calculating with GLI $H_{measured}$ (96.8±3.1 vs. 87.0±3.0 % predicted), and the same tendency could be noticed when calculating with ECCS and GLI using $H_{corrected}$ (99.5±3.5 vs. 90.6±3.1 % predicted). Similar results were obtained when comparing FEV1% between the 2 methods: using ECCS and GLI with $H_{measured}$, GLI resulted significantly lower

values (83.6±3.4 vs. 79.0±3.4 % predicted) as well as calculating with $H_{corrected}$ (85.7±3.7 vs 81.3±3.5 % predicted).

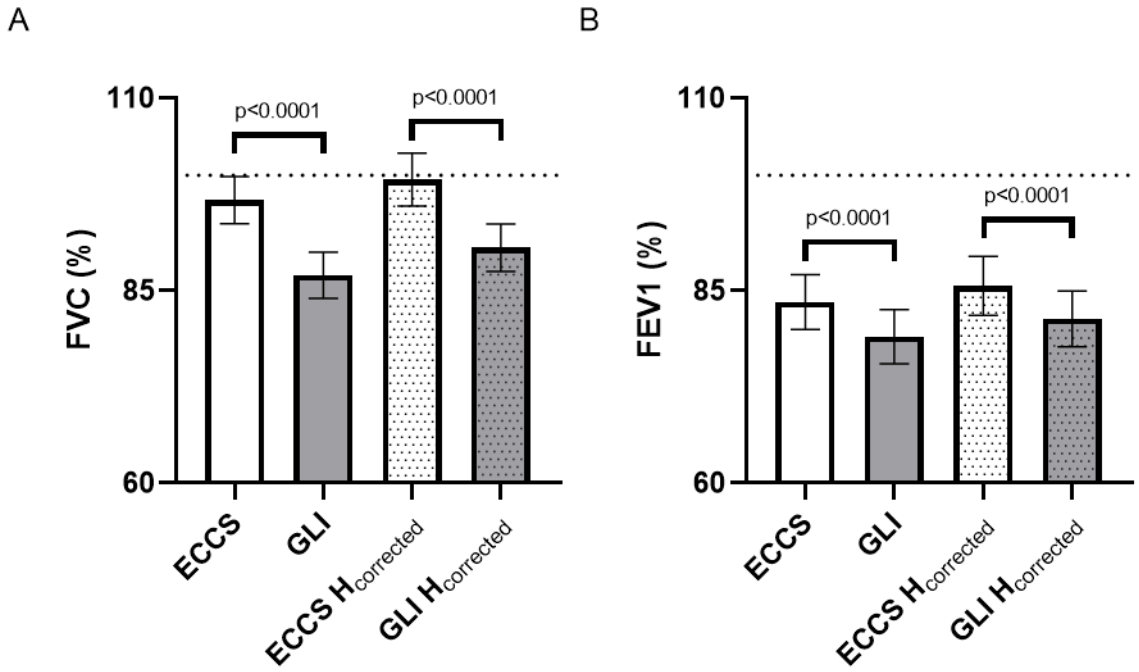


Figure 7. Comparison of FVC% (A) and FEV1% (B) values in MFS with and without height correction by using ECCS and GLI. The dotted lines represent 100%.

Data were presented as mean ± standard error of the mean.

5. Discussion

MFS is a connective tissue disorder that can affect many organ systems and manifests itself in a wide variety of symptoms during all phases of life [180, 181]. Our study has the largest cohort of patients with MFS who have been fully assessed for respiratory involvement and whose LF results have been evaluated with 2 different reference equations. More than 20% of the whole patient group had pulmonary complaints. Cough, shortness of breath and chest pain were common, mainly observable in Mf_{op} patients. Quality of life test results correlated with the symptoms.

LF values are usually based on age, sex and standing height, which may be misleading in MFS, where the length of the lower limbs contributes disproportionally to height [182]. We used $H_{corrected}$ to overcome the height measurement bias. It resulted in a significant reduction in the standing height values of MFS patients, which led to significant shrinkage in the LF results in the Mf group, mainly in men. This led us to the conclusion that in many MFS patients the standard and widely used LF reference equations underestimate the LF values of these patients.

In 1960, the ECCS was the first organisation to release recommendations for the calculation of reference values [145]. These reference values were based on male coal miners and steel workers. This was not a representative basis as reference and later in practice the predicted values were considered to be too high. Besides, no women had been tested and ECCS calculated the reference values for females by using 80% of the values for men [144].

Our data confirmed airway obstruction in MFS, mainly affecting the lower airways. Similar result had been previously published by Streeten et al. [76]. It has a great clinical importance to ensure suitable LF testing during or following extensive thoracic interventions. As a majority of Mf_{op} patients had scoliosis, it is not surprising that the measured and corrected heights did not differ in these patients. However, calculating with $H_{corrected}$ it revealed abnormal FVC% and FEV1% values. The moderate airway obstruction in this young patient population might be a consequence of connective tissue malfunction. In the background early emphysema and/or increased tendency towards airway collapse might be suspected [77]. Due to the aberrant structure of FBN-1, emphysema is a common finding in MFS. Robbesom et al. demonstrated the that an

aberrant FBN-1 staining in lung specimens was significantly associated with the three most important morphometric parameters for emphysema: alveolar destruction, the airspace enlargement, and the emphysema-related morphological abnormalities [183]. Experimental data in murine models proved widening of the distal airspaces in MFS, as well [184]. Hogg et al. described that emphysema affects mainly those parts of the lungs, where obstruction is pronounced; areas with trapped air may develop emphysema over time [185, 186]. In MFS there is a tendency for small airway collapse. It can be assumed that due to the connective tissue weakness, air trapping starts in the small airways and later develops into emphysema. From the 55 patients 6 had asthma, 5 of them were well-controlled (Mf n=3, Mf_{op} n=2) and had no respiratory changes at the time of our assessment. One patient waiting for MTS had mixed ventilatory pattern. Scoliosis appears frequently in MFS, and most often may cause restrictive ventilatory defect due to the anatomical distortion of the chest, resulting in reduced lung volumes [187]. It is unusual, but literature also mentions bronchial obstruction, caused by the compression of the deformed spine [188]. In our patients, the grade of scoliosis showed significant negative correlation with FVC% and FEV1%, implying restrictive changes due to thorax abnormalities. Shortly after the publication of our results regarding the correlation between LF values and scoliosis, a study performed in children with MFS confirmed these findings [75, 189].

LF evaluation in patients with atypical anthropometrical features can be difficult. The equations used in LF testing might give different results and it would be beneficial to reassess results in those who have unusual physical features.

As of the time, the reference equations available for the estimation of LF results have had several inaccuracies: they are often based on rather weak samples of normal individuals; they use mathematical models that are not effective in describing the changes of LF over age; there are different equations for children, adolescents and for adults: they define the results only as %predicted and do not provide a good indication of the statistical significance of any difference that may exist between a measured values and its reference values. GLI does not have these disadvantages. The GLI equations are used to define a reference value, LLN as threshold value and a z-score that takes age, sex, size and, for some LF calculations, ethnicity into account [190]. Several studies concluded that GLI seems to be the most accurate method for the evaluation of LF results [191–193].

Regarding LF parameters, GLI seems to be more adequate as compared to other reference equations regardless of sex, age, ethnicity and anthropometric features. In the Swedish CArdioPulmonary bioImage Study (SCAPIS) the DLCO values of healthy partakers were examined. As conclusion, SCAPIS reported that their findings emphasise the clinical importance of adequate reference values and the need of evaluating the GLI-based reference values in specific populations [194]. Other studies supported the advantages of using GLI reference equations, as well [195].

To evaluate the adequacy of the ECCS reference equation in our patient group, we selected 32 MFS patients who had no respiratory symptoms. One-fourth of these patients had airway obstruction, 28% showed restrictive ventilatory pattern including 9%, who had mixed ventilatory disorder. Mixed functional abnormalities are defined in the guideline when FEV1/VC and TLC are below the 5th percentiles of their relevant predicted values [147]. We recalculated their LF results by using GLI reference equations, as - based on the above outlined benefits regarding literature data – we considered that they might be useful in our patient group as well. In our research we proved that with the use of GLI LLN over FEV1/FVC appeared to be more appropriate in the definition of subclinical airway obstruction, especially in MFS men. When interpreting spirometric data, measured values are expressed as percent of predicted. This method may be applied after the recommendation of Bates and Christie, who declared that a suitable general rule is that a deviation of 20% from the predicted normal value is most likely significant [196]. Eighty percent is commonly accepted as LLN, but it is only valid if the scatter around the predicted value is proportional to the value itself: small, if the value is small and proportionally larger is it the predicted value is larger [144]. In contrast, respiratory data lack proportionality, which leads to inappropriate interpretation of the results [146, 148, 157, 197–199]. In 2012 Quanjer et al. urged the necessity of more precise LF calculations [200, 201]. Potential misidentification of respiratory disease, especially in aging population is of major public health concern. Previous studies in more than 10000 COPD patients (*COPDGene*) emphasizes the importance of GLI defined Z-score of 1.64 defining LLN at the 5^{th} percentile of distribution [131]. As an example, GLI defined normal values suggested the absence of clinically meaningful respiratory disease compared to Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry classification. Discordant classification by GOLD but normal LLN might result in

misidentification of emphysema as COPD [202]. Graded associations were found between the type and severity of GLI-defined spirometric impairment and respiratory-related phenotypes, including dyspnoea, poor respiratory health-related quality of life, poor exercise performance, bronchodilator reversibility, and computed tomography–diagnosed emphysema and gas trapping. These results suggest that GLI-defined spirometric impairment establishes clinically meaningful respiratory disease [200]. In the background cardiovascular mechanism, respiratory muscle weakness, obesity and kyphoscoliosis were identified as possible contributors. In our study individual presentation of LF values using the two reference equations were discordant in 6.3%, while concordant data were seen in 21.9% for airway obstruction. FVC% decline as a marker of restrictive ventilatory disorder was present in only 4 patients using ECCS while 28.1% (n=9) were under LLN using GLI reference. Identification of mixed ventilatory disorder was more common when using GLI 9.4% (n=3). Several prediction equations are based on data collected decades ago, leading to inaccurate LF results in many patient groups [144]. It was considered being too difficult to calculate the LLN for the FEV1/FVC, thus the GOLD group decided that it was easier to adopt a fixed LLN of 0.7 and a lot of criticism has been published about the unscientific method and the lack of evidence that obstructive lung disease using fixed LLN can be properly diagnosed [148, 201, 202]. This can lead to false negative finding regarding the prevalence of obstructive lung diseases, particularly in younger individuals, while to higher prevalence in older patients [144]. GLI uses a unified method interpreting LF in different races across all ages and sexes [148]. In adults FEV1/FVC ratios differ from those of GLI as compared to ECCS [205]. This is mainly due to the fact that GLI equations consider that the ratio is inversely related to standing height, while the ECCS equations take only age into account. This was also supported by the study of Kuster et al. This study also endorses the use of arm span to evaluate height, e.g. in case of e conditions that hamper the standing position [206]. Hence, GLI reference equations should be used instead of the ECCS predicted values as it already has been validated in several studies [207, 208]. Patients with special anthropometric feature, like MFS patients, may have false positive or false negative values if extrapolations are distorted by height [75]. In our research we applied two methods to calculate the LFs: ECCS and GLI calculations and the results were more consistent with the use of GLI. This agrees with the findings of Stanojevic et al., and is

also subsequently endorsed by the ATS and other respiratory societies worldwide [148]. Important to note that individuals with MFS are more prone to airway obstruction and by using GLI FEV1% was more sensitive to detect early changes in asymptomatic, young patients, especially in men. Fragoso et al. observed that GLI often defined normal (>LLN) spirometry in patients classified as COPD by GOLD [200].

In MFS, sensitive LF reference equations are crucial due to the special physical features. Kyphoscoliosis and emphysema often result in mixed (restrictive-obstructive) ventilatory defect in MFS [209]. Our data confirmed that GLI is more sensitive to detect airway obstruction in patients with unique anatomic properties and should be used as standard way of evaluation as compared to height correction in MFS. With the application of GLI calculation method, the daily clinical practice in respiratory care can be improved and it can be applied for patient groups with uncommon physical characteristics.

A future imaging study is planned in order to analyse the extent of air trapping and emphysema in our patients with MFS. Longitudinal evaluation of LF using GLI would be also beneficial to assess the lung aging process in MFS.

6. Conclusions

We investigated the LF changes with complex respiratory functional assessment of a large cohort of MFS. Based on the results described above, the following conclusions were made:

1. Chest deformities appeared in more than 70% of the patients and were more frequent in the Mf_{op} group as in Mf patients, while pulmonary complaints emerged in 20% of the patients and were also more common in Mf_{op} partakers.

2. LF changes were more common in Mf_{op} patients as compared to the Mf group and airway obstruction occurred more frequently in the Mf_{op} group compared to the Mf group.

3. Height correction revealed decreased FVC% and FEV1% values in Mfop patients compared to Mf patients more in line with their clinical symptoms.

4. There is a negative correlation between the extent of scoliosis and the FVC% and FEV1% results.

5. The use of GLI LLN for FEV1/FVC appeared to be more appropriate in the definition of subclinical airway obstruction, as compared to ECCS reference values, especially in MFS men.

6. With the use of GLI methodology, significantly lower FVC% and FEV1% values were proved as compared to the originally measured LF results and was less sensitive for height correction. In contrast, when calculating with ECCS $H_{measured}$ and ECCS $H_{corrected}$, the data were incongruent and were not in line with the clinical characteristics of MFS.

7. Summary

MFS has diverse systemic manifestations. Beside musculoskeletal and cardiovascular alterations, respiratory changes are also common. [210] Due to the special anthropometric features of the patients (tall, thin physique), LF testing is particularly challenging in this patient group. [211] Only scarce literature data is available about the LF changes in MFS and none of them had fully investigated the pulmonological abnormalities.

Our aim was to maximize the accuracy of the respiratory evaluation in patient with MFS, as it has a great clinical importance, e.g. in the preoperative assessment of their respiratory status and in the follow-up of their condition.

There was a significant difference in the frequency of pulmonary complaints, symptoms and LF values between Mf and Mf_{op} patients: Mf_{op} patients had significantly more complaints and pleuropulmonary symptoms as compared to Mf group, which highlights the importance of close follow-up after MTS in these patients.

Extrapolation of $H_{corrected}$ from the arm span of MFS patients was also performed, after which LF values were recalculated in every individual using $H_{corrected}$. Increased LF results could be seen in every patient group after the correction, however FEV1% still stayed in the pathological range in Mf_{op} patients.

The grade of scoliosis was also measured in every patient. Correlation analysis confirmed a negative correlation between the extent of scoliosis and the FVC% and FEV1% values after height correction.

Following the re-evaluation of the LF results in every MFS patient who had no pulmonary complaints, we could determine that GLI is more suitable to detect asymptomatic airway obstruction, especially in men. GLI results are also more in line with the clinical severity of the disease.

Based on these data, we propose carefully organized LF measurements and the use of GLI methodology in patients with special anthropometric features.

8. References

[1] D. P. Judge and H. C. Dietz. (2005) Marfan's syndrome. *Lancet*, vol. 366, no. 9501 pp. 1965–1976. doi: 10.1016/S0140-6736(05)67789-6.

[2] A. Marfan. *Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement*. Paris: Impr. Maretheux, 1896.

[3] B. Lee, M. Godfrey, E. Vitale, H. Hori, M. G. Mattei, M. Sarfarazi, P. Tsipouras, F. Ramirez, and D. W. Hollister. (1991) Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes. *Nature*, vol. 352, no. 6333 pp. 330–4. doi: 10.1038/352330a0.

[4] M. E. Colovati, L. R. da Silva, S. S. Takeno, T. I. Mancini, A. R. N Dutra, R. S. Guilherme, C. B. de Mello, M. I. Melaragno, and A. B. A Perez. (2012) Marfan syndrome with a complex chromosomal rearrangement including deletion of the FBN1 gene. *Mol. Cytogenet.*, vol. 5 p. 5. doi: 10.1186/1755-8166-5-5.

[5] The FBN1 mutations database. . http://www.umd.be/FBN1/.

[6] C. L. Maslen, G. M. Corson, B. K. Maddox, R. W. Glanville, and L. Y. Sakai. (1991) Partial sequence of a candidate gene for the Marfan syndrome. *Nature*, vol. 352, no. 6333 pp. 334–337. doi: 10.1038/352334a0.

[7] G. M. Corson, S. C. Chalberg, H. C. Dietz, N. L. Charbonneau, and L. Y. Sakai. (1993) Fibrillin Binds Calcium and Is Coded by cDNAs That Reveal a Multidomain Structure and Alternatively Spliced Exons at the 5′ End. *Genomics*, vol. 17, no. 2 pp. 476–484. doi: 10.1006/geno.1993.1350.

[8] L. Y. Sakai, D. R. Keene, M. Renard, and J. De Backer. (2016) FBN1: The disease-causing gene for Marfan syndrome and other genetic disorders. *Gene*, vol. 591, no. 1 pp. 279–291. doi: 10.1016/j.gene.2016.07.033.

[9] Fibrillin puzzle a step closer to completion Page - Department of Biochemistry, University of Oxford. . http://web.archive.org/web/20160311120126/http://www.bioch.ox.ac.uk/aspsite/index.asp?pageid=656. (Accessed: 2017.)

[10] L. Pereira, K. Andrikopoulos, J. Tian, S. Y. Lee, D. R. Keene, R. Ono, D. P. Reinhardt, L. Y. Sakai, N. J. Biery, T. Bunton, H. C. Dietz, and F. Ramirez. (1997)

Targetting of the gene encoding fibrillin–1 recapitulates the vascular aspect of Marfan syndrome. *Nat. Genet.*, vol. 17, no. 2 pp. 218–222. doi: 10.1038/ng1097-218.

[11] R. P. Mecham and J. E. Heuser. The Elastic Fiber. , in *Cell Biology of Extracellular Matrix*, Boston, MA: Springer US, 1991, pp. 79–109. .

[12] H. C. Dietz and R. E. Pyeritz. (1995) Mutations in the human gene for fibrillin-1 (FBN1) in the Marfan syndrome and related disorders. *Hum. Mol. Genet.*, vol. 4 Spec No pp. 1799–809. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/8541880.

[13] C. Baldock, A. J. Koster, U. Ziese, M. J. Rock, M. J. Sherratt, K. E. Kadler, C. A. Shuttleworth, and C. M. Kielty. (2001) The Supramolecular Organization of Fibrillin-Rich Microfibrils. *J. Cell Biol.*, vol. 152, no. 5 pp. 1045–1056. doi: 10.1083/jcb.152.5.1045.

[14] R. N. M. Kumar Viney, K. Abul Abbas, Fausto Nelson. *Robbins: A patológia alapjai*, 8. kiadás. Budapest: Medicina Könyvkiadó Zrt., 2009:255.

[15] Humán fibrillin makromolekulát kódoló gének. . https://www.ncbi.nlm.nih.gov/gene/?term=fibrillin.

[16] L. Pereira, M. D'Alessio, F. Ramirez, J. R. Lynch, B. Sykes, T. Pangilinan, and J. Bonadio. (1993) Genomic organization of the sequence coding for fibrillin, the defective gene product in Marfan syndrome. *Hum. Mol. Genet.*, vol. 2, no. 10 p. 1762. (Accessed: 2016.) Available: http://www.ncbi.nlm.nih.gov/pubmed/8268958.

[17] M. Arslan-Kirchner, Y. von Kodolitsch, and J. Schmidtke. (2008) The importance of genetic testing in the clinical management of patients with Marfan syndrome and related disorders. *Dtsch. Arztebl. Int.*, vol. 105, no. 27 pp. 483–91. doi: 10.3238/arztebl.2008.0483.

[18] G. Collod-Béroud, C. Béroud, L. Ades, C. Black, M. Boxer, D. J. Brock, K. J. Holman, A. de Paepe, U. Francke, U. Grau, C. Hayward, H. G. Klein, W. Liu, L. Nuytinck, L. Peltonen, A. B. Alvarez Perez, T. Rantamäki, C. Junien, and C. Boileau. (1998) Marfan Database (third edition): new mutations and new routines for the software. *Nucleic Acids Res.*, vol. 26, no. 1 pp. 229–3. doi: 10.1093/NAR/26.1.229.

[19] J. A. Jones and J. S. Ikonomidis. (2010) The pathogenesis of aortopathy in marfan syndrome and related diseases. *Curr. Cardiol. Rep.*, vol. 12, no. 2 pp. 99–107. doi: 10.1007/s11886-010-0083-z.

[20] J. P. Habashi, D. P. Judge, T. M. Holm, R. D. Cohn, B. L. Loeys, T. K. Cooper, L. Myers, E. C. Klein, G. Liu, C. Calvi, M. Podowski, E. R. Neptune, M. K. Halushka, D. Bedja, K. Gabrielson, D. B. Rifkin, L. Carta, F. Ramirez, D. L. Huso, and H. C. Dietz. (2006) Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science (80-.).*, vol. 312, no. 5770 pp. 117–121. doi: 10.1126/science.1124287.

[21] H. Zhang, S. D. Apfelroth, W. Hu, E. C. Davis, C. Sanguineti, J. Bonadio, R. P. Mecham, and F. Ramirez. (1994) Structure and expression of fibrillin-2, a novel microfibrillar component preferentially located in elastic matrices. *J. Cell Biol.*, vol. 124, no. 5 pp. 855–863. doi: 10.1083/jcb.124.5.855.

[22] FBN2 fibrillin 2 - Gene - GTR - NCBI. . https://www.ncbi.nlm.nih.gov/gtr/genes/2201/. (Accessed: 2020.)

[23] P. N. Robinson and M. Godfrey. (2000) The molecular genetics of Marfan syndrome and related microfibrillopathies. *J Med Genet*, vol. 37, no. 1 pp. 9–25. [Online]. Available: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10633129.

[24] J. P. Meena, A. Gupta, D. Mishra, and M. Juneja. (2015) Beals–Hecht syndrome (congenital contractural arachnodactyly) with additional craniospinal abnormality. *J. Pediatr. Orthop. B*, vol. 24, no. 3 pp. 226–229. doi: 10.1097/BPB.0000000000000121.

[25] FBN3 gene and fibrillin-3. . https://www.ncbi.nlm.nih.gov/gene/84467.

[26] P. N. Robinson, E. Arteaga-Solis, C. Baldock, G. Collod-Beroud, P. Booms, A. De Paepe, H. C. Dietz, G. Guo, P. A. Handford, D. P. Judge, C. M. Kielty, B. Loeys, D. M. Milewicz, A. Ney, F. Ramirez, D. P. Reinhardt, K. Tiedemann, P. Whiteman, and M. Godfrey. (2006) The molecular genetics of Marfan syndrome and related disorders. *J. Med. Genet.*, vol. 43, no. 10 pp. 769–787. doi: 10.1136/jmg.2005.039669.

[27] I. El-Hamamsy and M. H. Yacoub. (2009) Cellular and molecular mechanisms of

thoracic aortic aneurysms. *Nat. Rev. Cardiol.*, vol. 6, no. 12 pp. 771–786. doi: 10.1038/nrcardio.2009.191.

[28] P. Arnaud, N. Hanna, M. Aubart, B. Leheup, S. Dupuis-Girod, S. Naudion, D. Lacombe, O. Milleron, S. Odent, L. Faivre, L. Bal, T. Edouard, G. Collod-Beroud, M. Langeois, M. Spentchian, L. Gouya, G. Jondeau, and C. Boileau. (2017) Homozygous and compound heterozygous mutations in the FBN1 gene: unexpected findings in molecular diagnosis of Marfan syndrome. *J. Med. Genet.*, vol. 54, no. 2 pp. 100–103. doi: 10.1136/jmedgenet-2016-103996.

[29] Cystic medial necrosis: pathological findings and clinical implications. . http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-76382011000100019 (Accessed: 2020).

[30] T. J. M. Schlatmann and A. E. Becker. (1977) Pathogenesis of dissecting aneurysm of aorta. *Am. J. Cardiol.*, vol. 39, no. 1 pp. 21–26. doi: 10.1016/S0002-9149(77)80005-2.

[31] Acute Aortic Dissection: Overview, Pathophysiology & Risk Factors, Prehospital Care. . https://emedicine.medscape.com/article/756835-overview (Accessed: 2020).

[32] V. Cañadas, I. Vilacosta, I. Bruna, and V. Fuster. (2010) Marfan syndrome. Part 1: pathophysiology and diagnosis. *Nat. Rev. Cardiol.*, vol. 7, no. 5 pp. 256–265. doi: 10.1038/nrcardio.2010.30.

[33] M. Nataatmadja, J. West, and M. West. (2006) Overexpression of Transforming Growth Factor- Is Associated With Increased Hyaluronan Content and Impairment of Repair in Marfan Syndrome Aortic Aneurysm. *Circulation*, vol. 114, no. 1 Suppl pp. I371-7. doi: 10.1161/CIRCULATIONAHA.105.000927.

[34] M. A. LYNAS. (1958) Marfan's Syndrome in Northern Ireland: an account of thirteen families. *Ann. Hum. Genet.*, vol. 22, no. 4 pp. 289–309. doi: 10.1111/j.1469-1809.1958.tb01423.x.

[35] H.-H. Chiu, M.-H. Wu, H.-C. Chen, F.-Y. Kao, and S.-K. Huang. (2014) Epidemiological Profile of Marfan Syndrome in a General Population: A National Database Study. *Mayo Clin. Proc.*, vol. 89, no. 1 pp. 34–42. doi: 10.1016/j.mayocp.2013.08.022.

[36] K. A. Groth, H. Hove, K. Kyhl, L. Folkestad, M. Gaustadnes, N. Vejlstrup, K.

Stochholm, J. R. Østergaard, N. H. Andersen, and C. H. Gravholt. (2015) Prevalence, incidence, and age at diagnosis in Marfan Syndrome. *Orphanet J. Rare Dis.*, vol. 10 p. 153. doi: 10.1186/s13023-015-0369-8.

[37] Marfan Syndrome - GeneReviews® - NCBI Bookshelf. . https://www.ncbi.nlm.nih.gov/books/NBK1335/ (Accessed 2020).

[38] B. J. Maron, B. R. Chaitman, M. J. Ackerman, A. Bayés de Luna, D. Corrado, J. E. Crosson, B. J. Deal, D. J. Driscoll, M. Estes, C. G. S. Araújo, D. H. Liang, M. J. Mitten, R. J. Myerburg, A. Pelliccia, P. D. Thompson, J. A. Towbin, S. P. Van Camp. (2004) Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation*, vol. 109, no. 22 pp. 2807–2816. doi: 10.1161/01.CIR.0000128363.85581.E1.

[39] Marfan Syndrome - Physiopedia. . https://www.physio-pedia.com/Marfan_Syndrome. (Accessed: 2020.)

[40] F. De Maio, A. Fichera, V. De Luna, F. Mancini, and R. Caterini. (2016) Orthopaedic Aspects of Marfan Syndrome: The Experience of a Referral Center for Diagnosis of Rare Diseases. *Adv. Orthop.*, vol. 2016 pp. 1–6. doi: 10.1155/2016/8275391.

[41] Child Growth Assessment. . https://www.childhealth-explanation.com/growth-assessment.html (Accessed 2020).

[42] Upper to Lower Segment Ratio. , in *Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine*, Springer Berlin Heidelberg, 2006, pp. 1972–1973. .

[43] P. Trobisch, O. Suess, and F. Schwab. (2010) Idiopathic Scoliosis. *Dtsch. Aerzteblatt Online*, vol. 107, no. 49 pp. 875–884. doi: 10.3238/arztebl.2010.0875.

[44] S. Fraser, A. Child, and I. Hunt. (Jan. 2018) Pectus updates and special considerations in Marfan syndrome. *Pediatr. Rep.*, vol. 9, no. 4doi: 10.4081/pr.2017.7227.

[45] C. A. Demetracopoulos and P. D. Sponseller. (2007) Spinal Deformities in Marfan Syndrome. *Orthop. Clin. North Am.*, vol. 38, no. 4 pp. 563–572. doi: 10.1016/j.ocl.2007.04.003.

[46] G. Ramlingam. (2015) Ghent Criteria an Aid to Diagnose Latent Systemic Diseases in Marfan Syndrome. *J. Clin. DIAGNOSTIC Res.*, vol. 9, no. 5 pp. ZJ01–

ZJ02. doi: 10.7860/JCDR/2015/11932.5906.

[47] K. B. Jones, P. D. Sponseller, G. Erkula, L. Sakai, F. Ramirez, H. C. Dietz, S. Kost-Byerly, K. H. Bridwell, and L. Sandell. (2007) Symposium on the musculoskeletal aspects of marfan syndrome: Meeting report and state of the science. *J. Orthop. Res.*, vol. 25, no. 3 pp. 413–422. doi: 10.1002/jor.20314.

[48] K. N. Joseph, H. A. Kane, R. S. Milner, N. L. Steg, M. B. Williamson, and J. R. Bowen. (1992) Orthopedic aspects of the Marfan phenotype. *Clin. Orthop. Relat. Res.*, no. 277 pp. 251–61. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/1555349.

[49] Pes Planus - StatPearls - NCBI Bookshelf. . https://www.ncbi.nlm.nih.gov/books/NBK430802/?report=reader. (Accessed: 2020.)

[50] D. Melchiorre, E. Pratelli, E. Torricelli, F. Sofi, R. Abbate, M. Matucci-Cerinic, G. Gensini, and G. Pepe. (2016) A group of patients with Marfan's syndrome, who have finger and toe contractures, displays tendons' alterations upon an ultrasound examination: are these features common among classical Marfan patients? *Intern. Emerg. Med.*, vol. 11, no. 5 pp. 703–711. doi: 10.1007/s11739-016-1399-5.

[51] K. V Chalam, S. K. Gupta, S. Vinjamaram, and V. a Shah. (2006) Clinicopathologic reports, case reports, and small case series. *Arch. Ophthalmol.*, vol. 119, no. 3 pp. 409–10. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/12617716.

[52] I. H. Maumenee. (1981) The eye in the Marfan syndrome. *Trans. Am. Ophthalmol. Soc.*, vol. 79 pp. 684–733. .

[53] M. Latasiewicz, C. Fontecilla, E. Millá, and A. Sánchez. (2016) Marfan syndrome: Ocular findings and novel mutations - In pursuit of genotype-phenotype associations. *Can. J. Ophthalmol.*, vol. 51, no. 2 pp. 113–118. doi: 10.1016/j.jcjo.2015.12.019.

[54] G. Pepe, B. Giusti, E. Sticchi, R. Abbate, and G. F. Gensini. (2016) Marfan syndrome : current perspectives. pp. 55–65. .

[55] M. Kinori, S. Wehrli, I. S. Kassem, N. F. Azar, I. H. Maumenee, and M. B. Mets. (2017) Biometry Characteristics in Adults and Children With Marfan Syndrome: From the Marfan Eye Consortium of Chicago. *Am. J. Ophthalmol.*, vol. 177 pp.

144–149. doi: 10.1016/j.ajo.2017.02.022.

[56] H. Esfandiari, S. Ansari, H. Mohammad-Rabei, and M. Mets. (2019) Management strategies of ocular abnormalities in patients with marfan syndrome: Current perspective. *J. Ophthalmic Vis. Res.*, vol. 14, no. 1 p. 71. doi: 10.4103/jovr.jovr_29_18.

[57] V. A. McKusick. (1955) The cardiovascular aspects of Marfan's syndrome: a heritable disorder of connective tissue. *Circulation*, vol. 11, no. 3 pp. 321–42. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/14352380.

[58] R. E. Pyeritz and M. A. Wappel. (1983) Mitral valve dysfunction in the Marfan syndrome. Clinical and echocardiographic study of prevalence and natural history. *Am. J. Med.*, vol. 74, no. 5 pp. 797–807. doi: 10.1016/0002-9343(83)91070-7.

[59] X. Gu, Y. He, Z. Li, J. Han, J. Chen, and J. V. (Ian) Nixon. (2015) Echocardiographic versus Histologic Findings in Marfan Syndrome. *Texas Hear. Inst. J.*, vol. 42, no. 1 pp. 30–34. doi: 10.14503/THIJ-13-3848.

[60] H. W. L. de Beaufort, S. Trimarchi, A. Korach, M. Di Eusanio, D. Gilon, D. G. Montgomery, A. Evangelista, A. C. Braverman, E. P. Chen, E. M. Isselbacher, T. G. Gleason, C. De Vincentiis, T. M. Sundt, H. J. Patel, and K. A. Eagle. (2017) Aortic dissection in patients with Marfan syndrome based on the IRAD data. *Ann. Cardiothorac. Surg.*, vol. 6, no. 6 pp. 633–641. doi: 10.21037/acs.2017.10.03.

[61] M. C. Porciani, M. Attanasio, V. Lepri, I. Lapini, G. Demarchi, L. Padeletti, G. Pepe, R. Abbate, and G. F. Gensini. (2004) [Prevalence of cardiovascular manifestations in Marfan syndrome]. *Ital. Heart J. Suppl.*, vol. 5, no. 8 pp. 647–652. .

[62] A. Savolainen, M. Kupari, L. Toivonen, I. Kaitila, and M. Viitasalo. (1997) Abnormal ambulatory electrocardiographic findings in patients with the Marfan syndrome. *J. Intern. Med.*, vol. 241, no. 3 pp. 221–6. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/9104435.

[63] F. Alpendurada, J. Wong, A. Kiotsekoglou, W. Banya, A. Child, S. K. Prasad, D. J. Pennell, and R. H. Mohiaddin. (2010) Evidence for Marfan cardiomyopathy. *Eur. J. Heart Fail.*, vol. 12, no. 10 pp. 1085–1091. doi: 10.1093/eurjhf/hfq127.

[64] R. Mando, D. Tim, A. DeCicco, J. Trivax, and I. Hanson. (2020) Master of the Masquerade: An Atypical Presentation of Acute Aortic Dissection. *Case Reports*

Cardiol., vol. 2020 pp. 1–4. doi: 10.1155/2020/5743985.

[65] W.-I. Yang, C.-Y. Shim, I.-J. Cho, H.-J. Chang, D. Choi, Y. Jang, N. Chung, S.-Y. Cho, and J.-W. Ha. (2010) Dyssynchronous Systolic Expansion of Carotid Artery in Patients with Marfan Syndrome. *J. Am. Soc. Echocardiogr.*, vol. 23, no. 12 pp. 1310–1316. doi: 10.1016/j.echo.2010.08.022.

[66] R. M. Campbell, S. Berger, and J. Drezner. (2009) Sudden cardiac arrest in children and young athletes: the importance of a detailed personal and family history in the pre-participation evaluation. *Br. J. Sports Med.*, vol. 43, no. 5 pp. 336–341. doi: 10.1136/bjsm.2008.050534.

[67] J. De Backer, B. Loeys, D. Devos, H. Dietz, J. De Sutter, and A. De Paepe. (2006) A critical analysis of minor cardiovascular criteria in the diagnostic evaluation of patients with Marfan syndrome. *Genet Med*, vol. 8, no. 7 pp. 401–408. doi: 10.1097/01.gim.0000223550.41849.e3\r00125817-200607000-00002 [pii].

[68] A. Saeyeldin, M. A. Zafar, C. A. Velasquez, K. Ip, A. Gryaznov, A. J. Brownstein, Y. Li, J. A. Rizzo, Y. Erben, B. A. Ziganshin, and J. A. Elefteriades. (2017) Natural history of aortic root aneurysms in Marfan syndrome. *Ann. Cardiothorac. Surg.*, doi: 10.21037/acs.2017.11.10.

[69] W. Hao, Y. Fang, H. Lai, Y. Shen, H. Wang, M. Lin, and L. Tan. (2017) Marfan syndrome with pneumothorax: case report and review of literatures. *J. Thorac. Dis.*, vol. 9, no. 12 pp. E1100–E1103. doi: 10.21037/jtd.2017.11.66.

[70] P. R. Cohen and P. Schneiderman. (1989) Clinical Manifestations of the Marfan Syndrome. *Int. J. Dermatol.*, vol. 28, no. 5 pp. 291–9. doi: 10.1111/j.1365-4362.1989.tb01347.x.

[71] Z. El Ouali, N. Id El Haj, S. Boubia, and M. Ridai. (2020) Pneumothorax spontané récidivant révélant un syndrome de Marfan. *Rev. Mal. Respir.*, vol. 37, no. 1 pp. 86–90. doi: 10.1016/j.rmr.2019.11.649.

[72] J. R. Wood, D. Bellamy, a H. Child, and K. M. Citron. (1984) Pulmonary disease in patients with Marfan syndrome. *Thorax*, vol. 39, no. 10 pp. 780–4. doi: 10.1136/thx.39.10.780.

[73] M. Neuville, G. Jondeau, B. Crestani, and C. Taillé. (2015) Manifestations respiratoires du syndrome de Marfan. *Rev. Mal. Respir.*, vol. 32, no. 2 pp. 173–181. doi: 10.1016/j.rmr.2014.06.030.

[74] A. G. Corsico, A. Grosso, B. Tripon, F. Albicini, E. Gini, A. Mazzetta, E. M. Di Vincenzo, M. E. Agnesi, E. Tsana Tegomo, V. Ronzoni, E. Arbustini, and I. Cerveri. (Jun. 2014) Pulmonary involvement in patients with Marfan Syndrome. *Panminerva Med.*, vol. 56, no. 2 pp. 177–82. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/24994580.

[75] A. M. Kolonics-Farkas, B. Agg, K. Benke, B. Odler, A. Bohacs, Z. Kovats, Z. Szabolcs, and V. Müller. (2019) Lung Function Changes are More Common in Marfan Patients Who Need Major Thoracic Surgery. *Lung*, doi: 10.1007/s00408-019-00236-1.

[76] E. Streeten. (1987) Pulmonary function in the Marfan syndrome. *Chest ...*, pp. 408–412. doi: 10.1378/chest.91.3.408.

[77] L. Giske, J. K. Stanghelle, S. Rand-Hendrikssen, V. Strøm, J.-E. Wilhelmsen, and C. Røe. (2003) Pulmonary function, working capacity and strength in young adults with Marfan syndrome. *J. Rehabil. Med.*, vol. 35, no. 5 pp. 221–8. doi: 10.1080/16501970306095.

[78] E. R. Neptune, P. A. Frischmeyer, D. E. Arking, L. Myers, T. E. Bunton, B. Gayraud, F. Ramirez, L. Y. Sakai, and H. C. Dietz. (2003) Dysregulation of TGF-β activation contributes to pathogenesis in Marfan syndrome. *Nat. Genet.*, vol. 33, no. 3 pp. 407–411. doi: 10.1038/ng1116.

[79] K. Jespersen, Z. Liu, C. Li, P. Harding, K. Sestak, R. Batra, C. A. Stephenson, R. T. Foley, H. Greene, T. Meisinger, B. T. Baxter, and W. Xiong. (2020) Enhanced Notch3 signaling contributes to pulmonary emphysema in a Murine Model of Marfan syndrome. *Sci. Rep.*, vol. 10, no. 1 p. 10949. doi: 10.1038/s41598-020-67941-3.

[80] B. Agg, K. Benke, B. Szilveszter, M. Pólos, L. Daróczi, B. Odler, Z. B. Nagy, F. Tarr, B. Merkely, and Z. Szabolcs. (2014) Possible extracardiac predictors of aortic dissection in Marfan syndrome. *BMC Cardiovasc. Disord.*, vol. 14, no. 1 p. 47. doi: 10.1186/1471-2261-14-47.

[81] J. A. N. Meester, A. Verstraeten, D. Schepers, M. Alaerts, L. Van Laer, and B. L. Loeys. (2017) Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. *Ann. Cardiothorac. Surg.*, vol. 6, no. 6 pp. 582–594. doi: 10.21037/acs.2017.11.03.

[82] R. Bergman, M. J. Nevet, H. Gescheidt-Shoshany, A. L. Pimienta, and E. Reinstein. (2014) Atrophic skin patches with abnormal elastic fibers as a presenting sign of the MASS phenotype associated with mutation in the fibrillin 1 gene. *JAMA dermatology*, vol. 150, no. 8 pp. 885–9. doi: 10.1001/jamadermatol.2013.10036.

[83] G. Nijbroek, S. Sood, C. A. Francomano, E. Bull, L. Pereira, F. Ramirez, R. E. Pyeritz, and H. C. Dietz. (1995) Fifteen Novel FBNI Mutations Causing Marfan Syndrome Detected by Heteroduplex Analysis of Genomic Amplicons. pp. 8–21. .

[84] T. Böker, T. T. Vanem, A. H. Pripp, S. Rand-Hendriksen, B. Paus, H. J. Smith, and R. Lundby. (2019) Dural ectasia in Marfan syndrome and other hereditary connective tissue disorders: a 10-year follow-up study. *Spine J.*, vol. 19, no. 8 pp. 1412–1421. doi: 10.1016/j.spinee.2019.04.010.

[85] S. N. Eom, D. C. Kim, K. N. Kim, and S. H. Kim. (2014) Marfan syndrome and symptomatic dural ectasia: A case report and literature review. *J. Genet. Med.*, vol. 11, no. 2 pp. 83–85. doi: 10.5734/JGM.2014.11.2.83.

[86] R. E. Pyeritz, E. K. Fishman, B. A. Bernhardt, and S. S. Siegelman. (1988) Dural ectasia is a common feature of the Marfan syndrome. *Am. J. Hum. Genet.*, vol. 43, no. 5 pp. 726–32. (Accessed: 2017.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/3189335.

[87] N. U. Ahn, P. D. Sponseller, U. M. Ahn, L. Nallamshetty, P. S. Rose, J. M. Buchowski, E. S. Garrett, B. S. Kuszyk, E. K. Fishman, and S. J. Zinreich. (2000) Dural ectasia in the Marfan syndrome: MR and CT findings and criteria. *Genet. Med.*, vol. 2, no. 3 pp. 173–9. doi: 10.1097/00125817-200005000-00003.

[88] A. M. Hollenberg, A. L. Baldwin, A. Mesfin, and H. Silberstein. (2018) Rupture of Giant Anterior Sacral Meningocele in a Patient with Marfan Syndrome: Diagnosis and Management. *World Neurosurg.*, vol. 119 pp. 137–141. doi: 10.1016/j.wneu.2018.07.249.

[89] J. G. Stone, L. L. Bergmann, R. Takamori, and D. J. Donovan. (2015) Giant pseudomeningocele causing urinary obstruction in a patient with Marfan syndrome. *J. Neurosurg. Spine*, vol. 23, no. 1 pp. 77–80. doi: 10.3171/2014.11.SPINE131086.

[90] T. P. Sunna, H. J. Westwick, F. Zairi, I. Berania, and D. Shedid. (2016) Successful management of a giant anterior sacral meningocele with an endoscopic cutting stapler: case report. *J. Neurosurg. Spine*, vol. 24, no. 5 pp. 862–6. doi: 10.3171/2015.8.SPINE15129.

[91] C. Hentzen, N. Turmel, C. Chesnel, F. Le Breton, S. Sheikh Ismael, and G. Amarenco. (2018) Urinary Disorders and Marfan Syndrome: A Series of 4 Cases. *Urol. Int.*, vol. 101, no. 3 pp. 369–371. doi: 10.1159/000484696.

[92] B. Loeys, L. Nuytinck, I. Delvaux, S. De Bie, and A. De Paepe. (2001) Genotype and phenotype analysis of 171 patients referred for molecular study of the fibrillin-1 gene FBN1 because of suspected Marfan syndrome. *Arch. Intern. Med.*, doi: 10.1001/archinte.161.20.2447.

[93] B. Loeys, J. De Backer, P. Van Acker, K. Wettinck, G. Pals, L. Nuytinck, P. Coucke, and A. De Paepe. (2004) Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. *Hum. Mutat.*, doi: 10.1002/humu.20070.

[94] G. Li, J. Yu, K. Wang, B. Wang, M. Wang, S. Zhang, S. Qin, and Z. Yu. (2014) Exome sequencing identified new mutations in a Marfan syndrome family. *Diagn. Pathol.*, vol. 9, no. 1 p. 25. doi: 10.1186/1746-1596-9-25.

[95] R. Howarth, C. Yearwood, and J. F. Harvey. (2007) Application of dHPLC for Mutation Detection of the Fibrillin-1 Gene for the Diagnosis of Marfan Syndrome in a National Health Service Laboratory. *Genet. Test.*, vol. 11, no. 2 pp. 146–152. doi: 10.1089/gte.2006.0514.

[96] C. C. Hung, S. Y. Lin, C. N. Lee, H. Y. Cheng, C. Y. Lin, C. H. Chang, H. H. Chiu, C. C. Yu, S. P. Lin, W. F. Cheng, H. N. Ho, D. M. Niu, and Y. N. Su. (2009) Identification of fibrillin-1 gene mutations in Marfan syndrome by high-resolution melting analysis. *Anal. Biochem.*, vol. 389, no. 2 pp. 102–106. doi: 10.1016/j.ab.2009.03.032.

[97] A. De Paepe, R. B. Devereux, H. C. Dietz, R. C. M. Hennekam, and R. E. Pyeritz. (1996) Revised diagnostic criteria for the Marfan syndrome. *Am. J. Med. Genet.*, vol. 62, no. 4 pp. 417–426. doi: 10.1002/(SICI)1096-8628(19960424)62:4<417::AID-AJMG15>3.0.CO;2-R.

[98] B. L. Loeys, H. C. Dietz, A. C. Braverman, B. L. Callewaert, J. De Backer, R. B.

Devereux, Y. Hilhorst-Hofstee, G. Jondeau, L. Faivre, D. M. Milewicz, R. E. Pyeritz, P. D. Sponseller, P. Wordsworth, and A. M. De Paepe. (2010) The revised Ghent nosology for the Marfan syndrome. *J. Med. Genet.*, vol. 47, no. 7 pp. 476–485. doi: 10.1136/jmg.2009.072785.

[99] Summary of Diagnostic Criteria | The Marfan Foundation. . https://www.marfan.org/dx/rules (2020).

[100] Y. Isekame, S. Gati, J. A. Aragon-Martin, R. Bastiaenen, S. R. Kondapally Seshasai, and A. Child. (2016) Cardiovascular management of adults with marfan syndrome. *Eur. Cardiol. Rev.* , vol. 11, no. 2 pp. 102–110. doi: 10.15420/ecr/2016:19:2.

[101] N. Herrick, C. Davis, L. Vargas, H. Dietz, and P. Grossfeld. (2017) Utility of Genetic Testing in Elite Volleyball Players with Aortic Root Dilation. *Med. Sci. Sport. Exerc.*, vol. 49, no. 7 pp. 1293–1296. doi: 10.1249/MSS.0000000000001236.

[102] A. C. Braverman. (1998) Exercise and the Marfan syndrome. *Med. Sci. Sport. Exerc.*, vol. 30, no. Supplement pp. S387–S395. doi: 10.1097/00005768-199810001-00007.

[103] B. L. Halpern, F. Char, J. L. Murdoch, W. B. Horton, and V. A. McKusick. (1971) A prospectus on the prevention of aortic rupture in the Marfan syndrome with data on survivorship without treatment. *Johns Hopkins Med. J.*, vol. 129, no. 3 pp. 123–9. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/5113220.

[104] M. A. Salim, B. S. Alpert, J. C. Ward, and R. E. Pyeritz. (1994) Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. *Am. J. Cardiol.*, vol. 74, no. 6 pp. 629–33. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/7915491.

[105] R. Rossi-Foulkes, M. J. Roman, S. E. Rosen, R. Kramer-Fox, K. H. Ehlers, J. E. O'Loughlin, J. G. Davis, and R. B. Devereux. (1999) Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. *Am. J. Cardiol.*, vol. 83, no. 9 pp. 1364–8. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/10235096.

[106] J. Shores, K. R. Berger, E. A. Murphy, and R. E. Pyeritz. (1994) Progression of

Aortic Dilatation and the Benefit of Long-Term β-Adrenergic Blockade in Marfan's Syndrome. *N. Engl. J. Med.*, vol. 330, no. 19 pp. 1335–1341. doi: 10.1056/NEJM199405123301902.

[107] M. Ladouceur, C. Fermanian, J.-M. Lupoglazoff, T. Edouard, Y. Dulac, P. Acar, S. Magnier, and G. Jondeau. (2007) Effect of Beta-Blockade on Ascending Aortic Dilatation in Children With the Marfan Syndrome. *Am. J. Cardiol.*, vol. 99, no. 3 pp. 406–409. doi: 10.1016/j.amjcard.2006.08.048.

[108] C. Dahlöf, E. Dimenäs, M. Kendall, and I. Wiklund. (1991) Quality of life in cardiovascular diseases. Emphasis on beta-blocker treatment. *Circulation*, vol. 84, no. 6 Suppl pp. VI108-18. (Accessed: 2017.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/1683605.

[109] C. Gleiter and J. Deckert. (Nov. 1996) Adverse CNS-Effects of Beta-Adrenoceptor Blockers. *Pharmacopsychiatry*, vol. 29, no. 06 pp. 201–211. doi: 10.1055/s-2007-979572.

[110] A. T. Yetman, R. A. Bornemeier, and B. W. McCrindle. (2005) Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the marfan syndrome. *Am. J. Cardiol.*, vol. 95, no. 9 pp. 1125–1127. doi: 10.1016/j.amjcard.2005.01.032.

[111] D. I. Silverman, K. J. Burton, J. Gray, M. S. Bosner, N. T. Kouchoukos, M. J. Roman, M. Boxer, R. B. Devereux, and P. Tsipouras. (1994) Life expectancy in the Marfan syndrome. *Am. J. Cardiol.*, vol. 75, no. 2 pp. 157–160. doi: 10.1016/S0002-9149(00)80066-1.

[112] D. Hernandez-Vaquero, J. Silva, A. Escalera, R. Álvarez-Cabo, C. Morales, R. Díaz, P. Avanzas, C. Moris, and I. Pascual. (2020) Life Expectancy after Surgery for Ascending Aortic Aneurysm. *J. Clin. Med.*, vol. 9, no. 3 p. 615. doi: 10.3390/jcm9030615.

[113] H. Bentall and A. De Bono. (1968) A technique for complete replacement of the ascending aorta. *Thorax*, vol. 23, no. 4 pp. 338–9. doi: 10.1136/THX.23.4.338.

[114] D. Saksena, Y. K. Mishra, S. Muralidharan, V. Kanhere, P. Srivastava, and C. P. Srivastava. (2019) Follow-up and management of valvular heart disease patients with prosthetic valve: a clinical practice guideline for Indian scenario. *Indian J. Thorac. Cardiovasc. Surg.*, vol. 35, no. January pp. 3–44. doi: 10.1007/s12055-

019-00789-z.

[115] R. De Paulis, R. Scaffa, A. Salica, L. Weltert, and I. Chirichilli. (2018) Biological solutions to aortic root replacement: valve-sparing versus bioprosthetic conduit. *J. Vis. Surg.*, vol. 4 pp. 94–94. doi: 10.21037/jovs.2018.04.12.

[116] M. Ouzounian, V. Rao, C. Manlhiot, N. Abraham, C. David, C. M. Feindel, and T. E. David. Valve-Sparing Root Replacement Compared With Composite Valve Graft Procedures in Patients With Aortic Root Dilation. , 2016, doi: 10.1016/j.jacc.2016.07.767.

[117] C. Martín, A. Evangelista, S. Serrano-Fiz, S. Villar, V. Ospina, D. Martínez, J. De Villarreal, V. Sanchez, V. Moñivas, S. Mingo, and A. Forteza. (2020) Aortic Complications in Marfan Syndrome: Should We Anticipate Preventive Aortic Root Surgery?. *Ann. Thorac. Surg.*, vol. 109, no. 6 pp. 1850–1857. doi: 10.1016/j.athoracsur.2019.08.096.

[118] D. P. Judge and H. C. Dietz. (2008) Therapy of Marfan syndrome. *Annu. Rev. Med.*, vol. 59 pp. 43–59. doi: 10.1146/annurev.med.59.103106.103801.

[119] J. L. Murdoch, B. A. Walker, B. L. Halpern, J. W. Kuzma, and V. A. McKusick. (1972) Life Expectancy and Causes of Death in the Marfan Syndrome. *N. Engl. J. Med.*, vol. 286, no. 15 pp. 804–808. doi: 10.1056/NEJM197204132861502.

[120] R. E. Pyeritz. Marfan syndrome: improved clinical history results in expanded natural history. , *Genetics in Medicine*. 2019, doi: 10.1038/s41436-018-0399-4.

[121] M. Groenink, T. A. J. Lohuis, J. G. P. Tijssen, M. S. J. Naeff, R. C. M. Hennekam, E. E. Van Der Wall, and B. J. M. Mulder. (1999) Survival and complication free survival in Marfan's syndrome: Implications of current guidelines. *Heart*, vol. 82, no. 4 pp. 499–504. doi: 10.1136/hrt.82.4.499.

[122] G. L. Ruppel and P. L. Enright. (2012) Pulmonary function testing. *Respir. Care*, vol. 57, no. 1 pp. 165–175. doi: 10.4187/respcare.01640.

[123] B. G. Cooper, J. Stocks, G. L. Hall, B. Culver, I. Steenbruggen, K. W. Carter, B. R. Thompson, B. L. Graham, M. R. Miller, G. Ruppel, J. Henderson, C. A. Vaz Fragoso, and S. Stanojevic. (2017) The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe*, vol. 13, no. 3 pp. e56–e64. doi: 10.1183/20734735.012717.

[124] P. H. Quanjer, D. J. Brazzale, P. W. Boros, and J. J. Pretto. (2013) Implications of

adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. *Eur. Respir. J.*, vol. 42, no. 4 pp. 1046–1054. doi: 10.1183/09031936.00195512.

[125] M. Rosenfeld, M. S. Pepe, G. Longton, J. Emerson, S. FitzSimmons, and W. Morgan. (2001) Effect of choice of reference equation on analysis of pulmonary function in cystic fibrosis patients. *Pediatr. Pulmonol.*, vol. 31, no. 3 pp. 227–237. doi: 10.1002/ppul.1033.

[126] S. Stanojevic, A. Wade, S. Lum, and J. Stocks. (2007) Reference equations for pulmonary function tests in preschool children: A review. *Pediatr. Pulmonol.*, vol. 42, no. 10 pp. 962–972. doi: 10.1002/ppul.20691.

[127] P. Subbarao, P. Lebecque, M. Corey, and A. L. Coates. (2004) Comparison of spirometric reference values. *Pediatr. Pulmonol.*, vol. 37, no. 6 pp. 515–522. doi: 10.1002/ppul.20015.

[128] Y. Kwun, S. J. Kim, J. Lee, T. Isojima, D.-S. Choi, D.-K. Kim, J. Huh, I. Kang, M. Chang, S. Y. Cho, Y. B. Sohn, S. W. Park, and D.-K. Jin. (2015) Disease-specific Growth Charts of Marfan Syndrome Patients in Korea. *J. Korean Med. Sci.*, vol. 30, no. 7 p. 911. doi: 10.3346/jkms.2015.30.7.911.

[129] A. Talaminos Barroso, E. Márquez Martín, L. M. Roa Romero, and F. Ortega Ruiz. Factors Affecting Lung Function: A Review of the Literature. , *Archivos de Bronconeumologia*. 2018, doi: 10.1016/j.arbres.2018.01.030.

[130] X. Wang, D. W. Dockery, D. Wypij, M. E. Fay, and B. G. Ferris. (1993) Pulmonary function between 6 and 18 years of age. *Pediatr. Pulmonol.*, vol. 15, no. 2 pp. 75–88. doi: 10.1002/ppul.1950150204.

[131] S. Stanojevic, A. Wade, J. Stocks, J. Hankinson, A. L. Coates, H. Pan, M. Rosenthal, M. Corey, P. Lebecque, and T. J. Cole. (2008) Reference ranges for spirometry across all ages: A new approach. *Am. J. Respir. Crit. Care Med.*, vol. 177, no. 3 pp. 253–260. doi: 10.1164/rccm.200708-1248OC.

[132] D. R. Robbins, P. L. Enright, and D. L. Sherrill. (1995) Lung function development in young adults: is there a plateau phase?. pp. 768–772. doi: 10.1183/09031936.95.08050768.

[133] H. A. M. Kerstjens, B. Rijcken, J. P. Scheuten, and D. S. Postma. (1997) Decline of FEV1 by age and smoking status: Facts, figures, and fallacies. *Thorax*, vol. 52,

no. 9 pp. 820–827. doi: 10.1136/thx.52.9.820.

[134] K. K. Byberg, I. B. Mikalsen, G. E. Eide, M. R. Forman, P. B. Júlíusson, and K. Øymar. (2018) The associations between weight-related anthropometrics during childhood and lung function in late childhood: A retrospective cohort study. *BMC Pulm. Med.*, vol. 18, no. 1doi: 10.1186/s12890-017-0567-3.

[135] J. N. Sancho-Chust, E. Chiner, A. Camarasa, and C. Senent. (2010) Differences in pulmonary function based on height prediction obtained by using alternative measures. *Respiration.*, vol. 79, no. 6 pp. 461–468. doi: 10.1159/000235862.

[136] A. Kjensli, M. Ryg, J. A. Falch, G. Armbrecht, L. M. Diep, E. F. Eriksen, and I. Ellingsen. (2010) Does body height reduction influence interpretation of lung function in COPD patients?. *Eur. Respir. J.*, vol. 36, no. 3 pp. 540–548. doi: 10.1183/09031936.00148609.

[137] Using arm span to evaluate standing height. . http://spirxpert.ers-education.org/en/spirometry/predicting-reference-values-for-all-ages/arm-span/ (Accessed: 2017).

[138] J. M. Parker, T. A. Dillard, and Y. Y. Phillips. (1996) Arm span-height relationships in patients referred for spirometry. *Am. J. Respir. Crit. Care Med.*, vol. 154, no. 2 pp. 533–536. doi: 10.1164/ajrccm.154.2.8756834.

[139] T. G. Babb, B. L. Wyrick, D. S. DeLorey, P. J. Chase, and M. Y. Feng. (2008) Fat distribution and end-expiratory lung volume in lean and obese men and women. *Chest*, doi: 10.1378/chest.07-1728.

[140] K. Parameswaran, D. C. Todd, and M. Soth. Altered respiratory physiology in obesity. , *Canadian Respiratory Journal*. 2006, doi: 10.1155/2006/834786.

[141] C. M. Salome, G. G. King, and N. Berend. Physiology of obesity and effects on lung function. , *Journal of Applied Physiology*. 2010, doi: 10.1152/japplphysiol.00694.2009.

[142] R. L. Jones and M. M. U. Nzekwu. (2006) The effects of body mass index on lung volumes. *Chest*, doi: 10.1378/chest.130.3.827.

[143] B. H. Culver, B. L. Graham, A. L. Coates, J. Wanger, C. E. Berry, P. K. Clarke, T. S. Hallstrand, J. L. Hankinson, D. A. Kaminsky, N. R. MacIntyre, M. C. McCormack, M. Rosenfeld, S. Stanojevic, and D. J. Weiner. (2017) Recommendations for a Standardized Pulmonary Function Report. An Official

American Thoracic Society Technical Statement. *Am. J. Respir. Crit. Care Med.*, vol. 196, no. 11 pp. 1463–1472. doi: 10.1164/rccm.201710-1981ST.

[144] P. H. Quanjer, S. Stanojevic, J. Stocks, and T. J. Cole. GLI-2012 reference values for spirometry GLI-2012 All-Age Multi-Ethnic Reference Values for Spirometry Advantages Consequences GLI-2012 reference values for spirometry Interpretation of spirometric data. (Accessed: 2018.) [Online]. Available: http://www.ers-education.org/lrmedia/2012/pdf/266696.pdf.

[145] D. Jouasset. (1961) Standardization of respiratory function tests in countries of the European Coal and Steel Community. *Minerva Med.*, vol. 16 pp. 1145–59. (Accessed: 2018.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/13790820.

[146] J. L. Hankinson, J. R. Odencrantz, and K. B. Fedan. (1999) Spirometric Reference Values from a Sample of the General U.S. Population. *Am J Respir Crit Care Med*, vol. 159 pp. 179–187. (Accessed: 2018.) [Online]. Available: https://www.atsjournals.org/doi/pdf/10.1164/ajrccm.159.1.9712108.

[147] R. Pellegrino, G. Viegi, V. Brusasco, R. O. Crapo, F. Burgos, R. Casaburi, A. Coates, C. P. M. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, M. R. Miller, D. Navajas, O. F. Pedersen, and J. Wanger. (2005) Interpretative strategies for lung function tests. *Eur. Respir. J.*, vol. 26, no. 5 pp. 948–968. doi: 10.1183/09031936.05.00035205.

[148] P. H. Quanjer, S. Stanojevic, T. J. Cole, X. Baur, G. L. Hall, B. H. Culver, P. L. Enright, J. L. Hankinson, M. S. M. Ip, J. Zheng, J. Stocks, and C. Schindler. (2012) Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *Eur. Respir. J.*, vol. 40, no. 6 pp. 1324–1343. doi: 10.1183/09031936.00080312.

[149] G. L. Hall and S. Stanojevic. The global lung function initiative (GLI) network ERS clinical research collaboration: How international collaboration can shape clinical practice. , *European Respiratory Journal*. 2019, doi: 10.1183/13993003.02277-2018.

[150] D. Brazzale, G. Hall, and M. P. Swanney. (2016) Reference values for spirometry and their use in test interpretation: A Position Statement from the Australian and New Zealand Society of Respiratory Science. *Respirology*, vol. 21, no. 7 pp. 1201–

1209. doi: 10.1111/resp.12855.

[151] S. Stanojevic, A. Wade, J. Stocks, J. Hankinson, A. L. Coates, H. Pan, M. Rosenthal, M. Corey, P. Lebecque, and T. J. Cole. (2008) Reference Ranges for Spirometry Across All Ages. *Am. J. Respir. Crit. Care Med.*, vol. 177, no. 3 pp. 253–260. doi: 10.1164/rccm.200708-1248OC.

[152] C. A. Vaz Fragoso, H. C. Cain, R. Casaburi, P. J. Lee, L. Iannone, L. S. Leo-Summers, and P. H. Van Ness. (2017) Spirometry, static lung volumes, and diffusing capacity. *Respir. Care*, vol. 62, no. 9 pp. 1137–1147. doi: 10.4187/respcare.05515.

[153] R. O. Crapo, A. H. Morris, and R. M. Gardner. (1981) Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am. Rev. Respir. Dis.*, doi: 10.1164/arrd.1981.123.6.659.

[154] R. J. Knudson, M. D. Lebowitz, C. J. Holberg, and B. Burrows. (1983) Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am. Rev. Respir. Dis.*, vol. 127, no. 6 pp. 725–734. doi: 10.1164/arrd.1983.127.6.725.

[155] P. L. Enright, R. A. Kronmal, M. Higgins, M. Schenker, and E. F. Haponik. (1993) Spirometry reference values for women and men 65 to 85 years of age: Cardiovascular Health Study. *Am. Rev. Respir. Dis.*, vol. 147, no. 1 pp. 125–133. doi: 10.1164/ajrccm/147.1.125.

[156] I. Cerveri, A. G. Corsico, S. Accordini, R. Niniano, E. Ansaldo, J. M. Antó, N. Künzli, C. Janson, J. Sunyer, D. Jarvis, C. Svanes, T. Gislason, J. Heinrich, J. P. Schouten, M. Wjst, P. Burney, and R. de Marco. (2008) Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax*, vol. 63, no. 12 pp. 1040–5. doi: 10.1136/thx.2008.095554.

[157] M. R. Miller, P. H. Quanjer, M. P. Swanney, G. Ruppel, and P. L. Enright. (2011) Interpreting Lung Function Data Using 80% Predicted and Fixed Thresholds Misclassifies More Than 20% of Patients. *Chest*, vol. 139, no. 1 pp. 52–59. doi: 10.1378/chest.10-0189.

[158] E. Hnizdo, H. W. Glindmeyer, E. L. Petsonk, P. Enright, and A. S. Buist. (2006) Case definitions for chronic obstructive pulmonary disease. *COPD J. Chronic Obstr. Pulm. Dis.*, doi: 10.1080/15412550600651552.

[159] M. P. Swanney, G. Ruppel, P. L. Enright, O. F. Pedersen, R. O. Crapo, M. R. Miller, R. L. Jensen, E. Falaschetti, J. P. Schouten, J. L. Hankinson, J. Stocks, and P. H. Quanjer. (2008) Using the lower limit of normal for the FEV 1 /FVC ratio reduces the misclassification of airway obstruction. doi: 10.1136/thx.2008.098483.

[160] F. García-Rio, J. B. Soriano, M. Miravitlles, L. Muñoz, E. Duran-Tauleria, G. Sánchez, V. Sobradillo, and J. Ancochea. (2011) Overdiagnosing subjects with COPD using the 0.7 fixed ratio: Correlation with a poor health-related quality of life. *Chest*, vol. 139, no. 5 pp. 1072–1080. doi: 10.1378/chest.10-1721.

[161] Y. Çolak, S. Afzal, B. G. Nordestgaard, J. Vestbo, and P. Lange. (2018) Young and middle-aged adults with airflow limitation according to lower limit of normal but not fixed ratio have high morbidity and poor survival: A population-based prospective cohort study. *Eur. Respir. J.*, doi: 10.1183/13993003.02681-2017.

[162] Magyar Marfan Alapítvány. . https://marfan.hu/ (Accessed: 2020).

[163] G. D. Pearson, R. Devereux, B. Loeys, C. Maslen, D. Milewicz, R. Pyeritz, F. Ramirez, D. Rifkin, L. Sakai, L. Svensson, A. Wessels, J. Van Eyk, and H. C. Dietz. (2008) Report of the national heart, lung, and blood institute and national marfan foundation working group on research in marfan syndrome and related disorders. *Circulation*, vol. 118, no. 7 pp. 785–791. doi: 10.1161/CIRCULATIONAHA.108.783753.

[164] K. Benke, B. Ágg, L. Szabó, B. Szilveszter, B. Odler, M. Pólos, C. Cao, P. Maurovich-Horvat, T. Radovits, B. Merkely, and Z. Szabolcs. (2016) Bentall procedure: quarter century of clinical experiences of a single surgeon. *J. Cardiothorac. Surg.*, vol. 11 p. 19. doi: 10.1186/s13019-016-0418-y.

[165] R. O. Crapo, R. Casaburi, A. L. Coates, P. L. Enright, N. R. MacIntyre, R. T. McKay, D. Johnson, J. S. Wanger, R. J. Zeballos, V. Bittner, and C. Mottram. (2002) ATS Statement. *Am. J. Respir. Crit. Care Med.*, vol. 166, no. 1 pp. 111–117. doi: 10.1164/ajrccm.166.1.at1102.

[166] M. R. Miller. (2005) Standardisation of spirometry. *Eur. Respir. J.*, vol. 26, no. 2 pp. 319–338. doi: 10.1183/09031936.05.00034805.

[167] Piston User Manual. , 2013. http://www.pistonmedical.com/Manuals/PDF/PDT111_EN_2013-07-26.pdf (Accessed: 2018).

[168] Measuring arm span. . http://spirxpert.ers-education.org/en/spirometry/technical-features-of-spirometric-measurements/measuring-arm-span/ (Accessed, 2017).

[169] W. Marek, E. M. Marek, K. Mückenhoff, H. Smith, and M. Kohlhäufl. (2011) Lung function in our aging population. pp. 108–114. doi: 10.1186/2047-783x-16-3-108.

[170] B. Cushen, N. Mccormack, K. Hennigan, I. Sulaiman, R. W. Costello, and B. Deering. (2016) A pilot study to monitor changes in spirometry and lung volume , following an exacerbation of Chronic Obstructive Pulmonary Disease (COPD), as part of a supported discharge program. *Respir. Med.*, vol. 119 pp. 55–62. doi: 10.1016/j.rmed.2016.08.019.

[171] P. W. Jones, G. Harding, P. Berry, I. Wiklund, W.-H. Chen, and N. Kline Leidy. (2009) Development and first validation of the COPD Assessment Test. *Eur. Respir. J.*, vol. 34, no. 3 pp. 648–654. doi: 10.1183/09031936.00102509.

[172] COPD Assessment Test (CAT) online. . https://www.catestonline.org/.

[173] S. L. Cheng, C. H. Lin, C. C. Wang, M. C. Chan, J. Y. Hsu, L. W. Hang, D. W. Perng, C. J. Yu, and H. C. Wang. (2019) Comparison between COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores for evaluation of clinical symptoms, comorbidities and medical resources utilization in COPD patients. *J. Formos. Med. Assoc.*, vol. 118, no. 1P3 pp. 429–435. doi: 10.1016/j.jfma.2018.06.018.

[174] J. C. Bestall, E. A. Paul, R. Garrod, R. Garnham, P. W. Jones, and J. A. Wedzicha. (1999) Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*, vol. 54, no. 7 pp. 581–586. doi: 10.1136/thx.54.7.581.

[175] G. Z. Heller, M. Manuguerra, and R. Chow. (2016) How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. *Scand. J. Pain*, vol. 13 pp. 67–75. doi: 10.1016/j.sjpain.2016.06.012.

[176] Spirometry Calculator. . http://gligastransfer.org.au/calcs/spiro.html (Accessed: 2019).

[177] H. Dietz. *Marfan Syndrome*. University of Washington, Seattle, 1993.

[178] G. Erkula, K. B. Jones, P. D. Sponseller, H. C. Dietz, and R. E. Pyeritz. (2002) Growth and maturation in Marfan syndrome. *Am. J. Med. Genet.*, vol. 109, no. 2

pp. 100–115. doi: 10.1002/ajmg.10312.

[179] S. Stanojevic, P. Quanjer, M. R. Miller, and J. Stocks. (2013) The Global Lung Function Initiative: Dispelling some myths of lung function test interpretation. *Breathe*, vol. 9, no. 6 pp. 462–474. doi: 10.1183/20734735.012113.

[180] A. D. Bitterman and P. D. Sponseller. (2017) Marfan Syndrome: A Clinical Update. *J. Am. Acad. Orthop. Surg.*, vol. 25, no. 9 pp. 603–609. doi: 10.5435/JAAOS-D-16-00143.

[181] S. G. Coelho and A. G. Almeida. (2020) Marfan syndrome revisited: From genetics to clinical practice. *Rev. Port. Cardiol. (English Ed.*, vol. 39, no. 4 pp. 215–226. doi: 10.1016/j.repce.2020.04.004.

[182] R. E. Pyeritz and V. A. McKusick. (1979) The Marfan Syndrome: Diagnosis and Management. *N. Engl. J. Med.*, vol. 300, no. 14 pp. 772–777. doi: 10.1056/NEJM197904053001406.

[183] A. A. Robbesom, M. M. Koenders, N. C. Smits, T. Hafmans, E. M. Versteeg, J. Bulten, J. H. Veerkamp, R. Dekhuijzen, and T. H. Van Kuppevelt. (2008) Aberrant fibrillin-1 expression in early emphysematous human lung: a proposed predisposition for emphysema. *Mod. Pathol.*, vol. 21, no. 10 pp. 297–307. doi: 10.1038/modpathol.3801004.

[184] J. J. Uriarte, T. Meirelles, D. Gorbenko Del Blanco, P. N. Nonaka, N. Campillo, E. Sarri, D. Navajas, G. Egea, and R. Farré. (2016) Early Impairment of Lung Mechanics in a Murine Model of Marfan Syndrome. doi: 10.1371/journal.pone.0152124.

[185] J. C. Hogg, P. T. Macklem, and W. M. Thurlbeck. (1967) The resistance of small airways in normal and diseased human lungs. *Aspen Emphysema Conf.*, vol. 10 pp. 433–41. (Accessed: 2018.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/5610792.

[186] J. C. Hogg, P. D. Paré, and T.-L. Hackett. (2017) The Contribution of Small Airway Obstruction to the Pathogenesis of Chronic Obstructive Pulmonary Disease. *Physiol. Rev.*, vol. 97, no. 2 pp. 529–552. doi: 10.1152/physrev.00025.2015.

[187] M. Qiabi, K. Chagnon, A. Beaupré, J. Hercun, and G. Rakovich. (2015) Scoliosis and bronchial obstruction. *Can. Respir. J.*, vol. 22, no. 4 pp. 206–208. doi:

10.1155/2015/640573.

[188] I. De Torres García, P. De Cabo Moreno, and A. M. G. Ramírez. (2013) Extrinsic bronchial obstruction caused by scoliosis. *Spine (Phila. Pa. 1976).*, vol. 38, no. 13 pp. 840–843. doi: 10.1097/BRS.0b013e31828f5419.

[189] H. Otremski, R. F. Widmann, M. F. Di Maio, and D. Ovadia. (2020) The correlation between spinal and chest wall deformities and pulmonary function in marfan syndrome. *J. Child. Orthop.*, vol. 14, no. 4 pp. 343–348. doi: 10.1302/1863-2548.14.200076.

[190] A. Guillien, T. Soumagne, J. Regnard, and B. Degano. (2018) The new reference equations of the Global Lung function Initiative (GLI) for pulmonary function tests. *Rev. Mal. Respir.*, vol. 35, no. 10 pp. 1020–1027. doi: 10.1016/j.rmr.2018.08.021.

[191] T. Madanhire, R. A. Ferrand, E. F. Attia, E. N. Sibanda, S. Rusakaniko, and A. M. Rehman. (2020) Validation of the global lung initiative 2012 multi-ethnic spirometric reference equations in healthy urban Zimbabwean 7-13 year-old school children: A cross-sectional observational study. *BMC Pulm. Med.*, vol. 20, no. 1 pp. 1–11. doi: 10.1186/s12890-020-1091-4.

[192] S. Sadiq, S. T. Ahmed, and B. Fawad. (2018) Collating Spirometry reference values in Asian children and Adolescents; puzzle out the reasons for variations. *Pakistan J. Med. Sci.*, vol. 34, no. 2 pp. 487–492. doi: 10.12669/pjms.342.14162.

[193] T. L. Blake, A. B. Chang, M. D. Chatfield, J. M. Marchant, and M. S. McElrea. (2020) Global Lung Function Initiative-2012 “other/mixed” spirometry reference equation provides the best overall fit for Australian Aboriginal and/or Torres Strait Islander children and young adults. *Respirology*, vol. 25, no. 3 pp. 281–288. doi: 10.1111/resp.13649.

[194] A. Malinovschi, X. Zhou, B. Bake, G. Bergström, A. Blomberg, J. Brisman, K. Caidahl, G. Engström, M. J. Eriksson, A. Frølich, C. Janson, K. Jansson, J. Vikgren, A. Lindberg, R. Linder, M. Mannila, H. L. Persson, C. Magnus Sköld, K. Torén, C. J. Östgren, P. Wollmer, and J. E. Engvall. (2020) Assessment of Global Lung Function Initiative (GLI) reference equations for diffusing capacity in relation to respiratory burden in the Swedish CArdioPulmonary bioImage Study (SCAPIS). *Eur. Respir. J.*, vol. 56, no. 2doi: 10.1183/13993003.01995-2019.

[195] D. J. Brazzale, L. M. Seccombe, L. Welsh, C. J. Lanteri, C. S. Farah, and W. R. Ruehland. (2020) Effects of adopting the Global Lung Function Initiative 2017 reference equations on the interpretation of carbon monoxide transfer factor. *Eur. Respir. J.*, vol. 55, no. 5doi: 10.1183/13993003.01905-2019.

[196] D. V. Bates and R. V. Christie. Respiratory Function in Disease. , 1st ed., W.B. Saunders, 1964, p. 91. .

[197] B. J. Sobol and B. Weinheimer. Assessment of ventilatory abnormality in the asymptomatic subject: an exercise in futility1., 1966.

[198] M. R. Miller and A. C. Pincock. (1988) Predicted values: how should we use them?. *Thorax*, vol. 43, no. 4 pp. 265–267. doi: 10.1136/thx.43.4.265.

[199] Lung Function Testing: Selection of Reference Values and Interpretative Strategies. (1991) *Am. Rev. Respir. Dis.*, vol. 144, no. 5 pp. 1202–1218. doi: 10.1164/ajrccm/144.5.1202.

[200] C. A. Vaz Fragoso, G. McAvay, P. H. Van Ness, R. Casaburi, R. L. Jensen, N. MacIntyre, H. K. Yaggi, T. M. Gill, and J. Concato. (2016) Phenotype of Spirometric Impairment in an Aging Population. *Am. J. Respir. Crit. Care Med.*, vol. 193, no. 7 pp. 727–735. doi: 10.1164/rccm.201508-1603OC.

[201] M. Xie, L. Cui, J. Liu, W. Wang, J. Li, and W. Xiao. (2020) Impacts of Different Spirometry Reference Equations and Diagnostic Criteria on the Frequency of Airway Obstruction in Adult People of North China. *Int. J. Chron. Obstruct. Pulmon. Dis.*, vol. Volume 15 pp. 651–659. doi: 10.2147/COPD.S232863.

[202] C.A.V. Fragoso (2018) Epidemiology of Chronic Obstructive Pulmonary Disease (COPD) in aging populations. vol. 13, no. 2 pp. 125–129. doi: 10.3109/15412555.2015.1077506.EPIDEMIOLOGY.

[203] P. H. Quanjer, P. L. Enright, M. R. Miller, J. Stocks, G. Ruppel, M. P. Swanney, R. O. Crapo, O. F. Pedersen, E. Falaschetti, J. P. Schouten, and R. L. Jensen. (2011) The need to change the method for defining mild airway obstruction. *Eur. Respir. J.*, vol. 37, no. 3 pp. 720–722. doi: 10.1183/09031936.00135110.

[204] P. H. Quanjer, P. L. Enright, M. R. Miller, J. Stocks, G. Ruppel, M. P. Swanney, R. O. Crapo, O. F. Pedersen, E. Falaschetti, and J. P. Schouten. (2010) The need to change the method for defining mild airway obstruction. *Prim. Care Respir. J.*, vol. 19, no. 3 pp. 288–291. doi: 10.4104/pcrj.2010.00052.

[205] P. H. Quanjer, G. J. Tammeling, J. E. Cotes, O. F. Pedersen, R. Peslin, and J. C. Yernault. (1993) Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur. Respir. J. Suppl.*, vol. 16 pp. 5–40. (Accessed: 2020.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/7973051.

[206] S. P. Kuster, D. Kuster, C. Schindler, M. K. Rochat, J. Braun, L. Held, and O. Brandli. (2008) Reference equations for lung function screening of healthy never-smoking adults aged 18-80 years. *Eur. Respir. J.*, vol. 31, no. 4 pp. 860–868. doi: 10.1183/09031936.00091407.

[207] S. Lum, R. Bonner, J. Kirkby, S. Sonnappa, and J. Stocks. (2012) S33 Validation of the GLI-2012 Multi-Ethnic Spirometry Reference Equations in London School Children. *Thorax*, vol. 67, no. Suppl 2 p. A18.2-A18. doi: 10.1136/thoraxjnl-2012-202678.039.

[208] G. L. Hall, B. R. Thompson, S. Stanojevic, M. J. Abramson, R. Beasley, A. Coates, A. Dent, B. Eckert, A. James, S. Filsell, A. W. B. Musk, G. Nolan, B. Dixon, C. O'Dea, J. Savage, J. Stocks, and M. P. Swanney. (2012) The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology*, vol. 17, no. 7 pp. 1150–1151. doi: 10.1111/j.1440-1843.2012.02232.x.

[209] B. Wang, X. Cao, Y. Qiu, B. Qian, X. Sun, A. Huang, Z. Zhu, Y. Yu, F. Zhu, and W. Ma. (2010) [Pulmonary dysfunction patterns in patients with Marfan and Marfanoid syndrome associated with scoliosis and the influencing factors]. *Zhonghua Wai Ke Za Zhi*, vol. 48, no. 9 pp. 686–9. (Accessed: 2016.) [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/20646552.

[210] I. Salik, P. Rawla. Marfan Syndrome. (2021) In: StatPearls [Internet]. Treasure Island (FL): PMID: 30726024. Available: https://pubmed.ncbi.nlm.nih.gov/30726024/

[211] A. Al Kaissi, E. Zwettler, R. Ganger, S. Schreiner, K. Klaushofer, and F. Grill. (2013) Musculo-Skeletal Abnormalities in Patients with Marfan Syndrome. *Clin. Med. Insights Arthritis Musculoskelet. Disord.*, vol. 6 p. CMAMD.S10279. doi: 10.4137/CMAMD.S10279.

9. Bibliography of the candidate's publications

Publications related to the present thesis

1. **Kolonics-Farkas AM**, Agg B, Benke K, Odler B, Bohacs A, Kovats Z, Szabolcs Z, Müller V. Lung Function Changes are More Common in Marfan Patients Who Need Major Thoracic Surgery. *Lung*, 2019 Aug;197(4):465-472. doi: 10.1007/s00408-019-00236-1. Epub 2019 May 14. PubMed PMID: 31089858; PubMed Central PMCID: PMC6647216.
   IF: 1.814
   Journal rank: Q2

2. **Kolonics-Farkas AM**, Kovats Z, Bohacs A, Odler B, Benke K, Agg B, Szabolcs Z, Müller V. Airway obstruction can be better predicted using Global Lung Function Initiative spirometry reference equations in Marfan syndrome. Physiol Int. 2021 Mar 25. doi: 10.1556/2060.2021.00002. Epub ahead of print. PMID: 33769955.
   IF: 1.41
   Journal rank: Q4

3. **Farkas A**, Odler B, Kováts Zs, Benke K, Ágg B, Szabolcs Z, Müller V. Pulmonális eltérések Marfan-szindrómás betegeknél. *Medicina Thoracalis*, 2017. Febr. 70. évf. 1.

10. Acknowledgements

First of all, I would like to express my sincere gratitude to Professor Veronika Müller, who gave me the opportunity to join her research group as a member of the Students' Scientific Association in 2015 and as a PhD student in 2017. She supported my work and professional development throughout the last 7 years and provided everything one needs in science: expertise, professional and personal advices, a well-equipped, peaceful and fair working environment.

I am indebted to Dr. Balázs Odler, who introduced me the colourful possibilities for professional development at the Department of Pulmonology and who helped my work at the beginning.

I would like to thank all the colleagues in the Department of Pulmonology, who were there to help me during my research, especially Dr. Anikó Bohács, Dr. Zsuzsanna Kováts, Dr. Krisztina Vincze and Dr. Noémi Eszes.

I am thankful to the fellow PhD students their helpful discussions.

I would like to thank the opportunity to Professor Zoltán Szabolcs, Dr. Kálmán Benke and Dr. Bence Ágg, that I could join their research and had the chance to work with this great patient group.

I am grateful to all the patients who participated in this study and helped my scientific work.

Finally, I would like to express my gratitude to my family, Ferenc, Lili and Sári for their unconditional emotional support and patience.