The Use of the Skeletal Burden Score for Predicting Physical Outcomes in Patients with Fibrous Dysplasia

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Declaration

I declare that the work in this thesis represents an original contribution to the field of research. The works herein were conducted and are presented in accordance with the requirements of the University of Sheffield's code of Practice for Research Degree Programme. All assistance or collaboration and sources of information and data used in this thesis have been acknowledged.

Arwa Alhulwah

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Abstract

Evaluating the extent of fibrous dysplasia (FD) is crucial for understanding the disease's severity, monitoring its progression, and effectively managing and treating its complications. The skeletal burden score (SBS) is the sole tool available for assessing FD severity that is unaffected by aging or the use of bisphosphonate treatment for bone pain. However, due to the rarity of FD and its diverse manifestations, there are a limited number of studies that have focused on the utilisation of SBS in the assessment of FD involvement.

This thesis presents a collection of original studies focusing on the applicability of SBS. The first two chapters were systematic reviews. The first one, investigated the SBS association with the quality of life (QoL) measures in FD patients. The second systematic review investigated the diagnostic accuracy of cross-sectional imaging modalities for the diagnosis of FD. We also measured the clinicians' knowledge and use of SBS through an internationally disseminated online survey.

The core research of this thesis involved conducting a multicentre study of FD/MAS patients from five collaborating sites in the United Kingdom and Saudi Arabia. The collected data were analysed to investigate three primary aims. First aim was to evaluate the agreement among five radiologists in measuring the SBS from bone scintigraphy scans presented in two different image formats. Second aim, to examine the quality of life (QoL) and highlighted the factors that influenced it, and to assess the relationship between SBS with the reported QoL and bone pain of the patient cohort. The third aim was to compare FD involvement on bone scintigraphy and whole-body magnetic resonance imaging (WB-MRI) scans. Also to evaluate the reliability of the SBS measured from WB-MRI scans, a novel approach.

Our longitudinal study highlighted the negative impact of FD on the QoL, in particular patients with extensive FD involvement. In addition, the SBS of the legs and pelvis compartments demonstrated a stronger correlation with the physical health domains of QoL than the total SBS. Excellent intra- and inter-reader agreement was observed among the readers and in using bone image formats. Also, good SBS reliability when measured from WB-MRI. Further research is required to validate our findings regarding the applicability of SBS on WB-MRI in a larger cohort.

Our findings offer insights into the accessibility of SBS for assessing the FD skeletal extent. This study aligns with the current international FD guidelines, emphasising the importance of using SBS to assess disease extent, and manage its complications to preserve physical health and QoL.

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In the name of Allah, the Most Gracious, the Most Merciful.

The completion of this thesis would not have been possible without the support of many individuals. First and foremost, I would like to express my deepest gratitude and appreciation to my supervisor Professor Amaka C. Offiah, who generously provided me with the knowledge and intellectual guidance throughout this PhD journey. Her unwavering patience and belief in me will always be cherished and remembered.

I also owe my deepest gratitude and appreciation to my second supervisor, Dr. Ashok Raghavan, for his positive input and for always pushing me to do my best. It has been a privilege and pleasure working under his supervision.

I would like to extend my gratitude to Professor Alan Rigby for providing the insightful statistical knowledge and supervision necessary for performing the statistical analysis throughout this thesis.

It has been an incredible experience collaborating with multiple sites across the United Kingdom and Saudi Arabia. I extend my deepest gratitude to Dr. Paul Arundel, Dr. James Fernandes, Dr. Jennifer Walsh, Prof. Kassim Javiad, Dr. Emad Al-Absi, Dr. Omar Salem, Dr. Abdulaziz AlSugair, Dr. Sarah AlShahwan, Dr. Afaf AlSagheir, Dr. Thamer AlHusainan, and all the nurses and administrators whose invaluable assistance made the completion of this study possible.

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Finally, I would like to thank Princess Nourah Bint Abdulrahman University for granting me the scholarship opportunity and funding my studies.

Collaborators Attribution

Professor Amaka C. Offiah, Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist, Sheffield Children's Hospital Foundation Trust, University of Sheffield, Sheffield, UK. Professor Offiah was the primary supervisor, the chief investigator of this study, and participated as a reader in Chapters 6, 7 and 8.

Dr Ashok Raghavan, Consultant Paediatric Radiologist, Sheffield Children's Hospital Foundation Trust, University of Sheffield, Sheffield, UK. Dr Raghavan was the secondary supervisor and participated as a reader in Chapters 6, 7 and 8.

Professor Alan Rigby, Chair of Statistics, University of Hull, Hull, UK. Professor Rigby supervised and provided guidance on the study's statistical analysis and the interpretation of the statistical findings.

Professor Kassim Javaid, Consultant Rheumatologist, Oxford University NHS Foundation Trust and lead investigator for the RUDY (Rare UK diseases study) registry. Professor Javaid was the study primary investigator at his collaborating site. And provided feedback in our study design and protocol.

Dr Paul Arundel, Consultant Paediatric Physician, Sheffield Children's Hospital Foundation Trust, Sheffield, UK. Dr Arundel reviewed the study protocol and led educational sessions on clinical practices related to the research topic.

Dr James Fernandes, Consultant Orthopaedic Surgeon, Sheffield Children's Hospital Foundation Trust, Sheffield, UK. Dr Fernandes led educational sessions on clinical practice in the orthopaedic clinic and introduced eligible patients to the study.

Dr Jennifer Walsh, Consultant Endocrinologist, Northern General Hospital, Sheffield, UK. Dr Walsh was the primary investigator for this study at her collaborating site. And identified and introduced eligible patients to the study.

Dr Abdulaziz Al Sugair, Consultant Nuclear Medicine Physician, King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia. Dr Al Sugair was the primary investigator for the study at his collaborating site. Also, a reader for the study arm covered in Chapter 6.

Dr Emad Al-Absi, Consultant Orthopaedic Surgeon, King Fahad Specialist Hospital, Dammam, Saudi Arabia. Dr Al-Absi was the primary investigator for the study at his collaborating site. Also identified and introduced the eligible patients to the study.

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Dr Riyadh AlSalloum, Consultant Radiologist, King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia. Dr AlSalloum participated as a reader in Chapter 6.

Dr Thamer Alhusainan, Consultant Orthopaedic surgeon, King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia. Dr Alhusainan identified and introduced eligible patients to the study.

Dr Afaf Alsagheir, Consultant Paediatrics Endocrinologist, King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia. Dr Alsagheir identified and introduced eligible patients to the study.

Dr Omar Salem, Consultant Orthopaedic surgeon, King Fahad Specialist Hospital, Dammam, Saudi Arabia. Dr Salem obtained consent from the participated patients and collected the data needed for this study.

Contributions

My contributions to this thesis are as follows:

- Drafted the study design, protocol, age-specific information sheets, and consent/assent forms.
- Established the inclusion and exclusion criteria for the study in the collaboration with the research team and based on their feedback.
- Recruited patients from the following sites: Sheffield Children's Hospital and Northern General Hospital in Sheffield, UK; King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia; and King Fahad Specialist Hospital in Dammam, Saudi Arabia.
- Administered consent forms and study information sheets, as well as collected outcome measures (quality of life and pain assessment questionnaires) at baseline and six-month follow-up.
- Collected demographic and clinical data from patients' electronic records and anonymised images according to the patients' assigned unique research IDs.
- Conducted statistical analysis across all study arms under the supervision and guidance of Professor Alan Rigby.
- Drafted and structured the study arms into a manuscript intended for future publication in peer-reviewed journals.

Conferences and poster presentations

Alhulwah, A.H, Raghavan, A., Shuweihdi, F., Offiah, A.C.," What Is the Correlation Between Skeletal Burden Score and Functional Outcome in Patients with Fibrous Dysplasia? A Systematic Review and Meta-Analysis". (Submitted and currently under review for publication in the peer-reviewed journal, *Quality of Life Research*)

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Dedication

With pride and affection, I dedicate this thesis to the memory of my late beloved father, ***Hammood****, who was the source of my inspiration, resilience, and passion for learning.*

I also dedicate this work to my mother, ***Hasna****, for her unwavering love, prayers, and encouragement in chasing my goals.*

To my beloved husband ***Abdulaziz****,*

and to my dear children ***Saud*** *and* ***Rayan****,*

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List of Abbreviations

ADC	Apparent Diffusion Coefficient
ALP	Alkaline Phosphatase
BA	Bland–Altman Plot
BTM	Bone Turnover Markers
BPI	Brief Pain Inventory
BMSC	Bone Marrow Mesenchymal Stromal Cells
cAMP	cyclic Adenosine Monophosphate
CT	Computed tomography
CTX	beta-C-Terminal Telopeptide
CI	Confidence Interval
DICOM	Digital Imaging and Communication in Medicine
DWI	Diffusion Weighted Imaging
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
FGF-23	Fibroblast Growth Factor-23
FD	Fibrous Dysplasia
FD/MAS	Fibrous Dysplasia/McCune-Albright Syndrome
18F-FDG	2-deoxy-2-[fluorine-18] fluoro-D-glucose
18F-NaF	[fluorine-18]- sodium fluoride
GNAS	Guanine Nucleotide-binding protein a-stimulating polypeptide
GH	Growth Hormone
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HU	Hounsfield Unit
ICC	Intraclass Correlation Coefficient
IGF-1	Insulin-like Growth Factor-1
IPQ-R	The Revised Illness Perception Questionnaire
IRAS	Integrated Research Application System
JPEG	Joint Photographic Experts Group
KFSH	King Fahad Specialist Hospital
KFSHRC	King Faisal Specialist Hospital & Research Centre
LUMC	Leiden University Medical Centre
MAS	McCune-Albright Syndrome
mSv	millisievert
MRI	Magnetic Resonance Imaging
MPQ	Multidimensional Personality Questionnaire
NPRS	Numeric Pain Rating Scale

NGH	Northen General Hospital
NGS	Next Generation Sequencing Testing
OUX	Oxford University Hospitals
PCR	Polymerase Chain Reaction
PedsQL	Paediatric Quality of Life Inventory
PET	Positron Emission Tomography
PODCI	Paediatric Outcomes Data Collection Instrument
PPQ	Paediatric Pain Questionnaire
PTH	Parathyroid Hormone
PICP	Procollagen I carboxyterminal Propeptide
P1NP	Total Procollagen 1 N-Terminal Propeptide
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	International Prospective Register of Systematic Reviews
QoL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
RANKL-RANK	Receptor Activator of Nuclear factor Kappa-B Ligand
RUDY	Rare UK Diseases Study
ROI	Region of interest
SA	Saudi Arabia
SBS	Skeletal Burden Score
SCH	Sheffield Children's Hospital
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
SF-36	36-Item Short-Form health survey
SPECT	Single Photon Emission Computed Tomography
SUV	Standardised Uptake Value
^{99m}Tc-HDP	Technetium 99m-hydroxy diphosphonate
^{99m}Tc-MDP	Technetium 99m-methyl diphosphonate
TH	Thyroid Hormone
UCL	Utrecht Coping List
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
VOI	Volume of Interest
WB-MRI	Whole-Body Magnetic Resonance Imaging

Chapter 1: Thesis Overview

1.1 Introduction

Fibrous dysplasia (FD) is a rare non-inherited metabolic bone disease characterised by the replacement of normal bone with benign fibro-osseus lesion, which can occur as single (monostotic) or multiple (polyostotic) lesions. The degree of disease severity varies widely, ranging from asymptomatic lesions discovered incidentally during radiological investigations for other abnormalities to severe cases causing physical impairment and necessitating the use of ambulatory assistive devices. Early evaluation of FD involvement is crucial for predicting outcomes and planning management strategies, particularly in cases with extensive lower-body FD involvement, to preserve future functional abilities.

In 2019, the first international guidelines for FD were published by a consortium of clinicians and experts. One of the key recommendations was the early evaluation of FD involvement in children as young as five years old, using a quantitative scoring tool called the skeletal burden score (SBS). The SBS, introduced by Dr Michael Collins in 2005, quantifies the FD skeletal involvement. Since its introduction, many studies have used the SBS as a reliable tool to assess the skeletal severity in patients with different FD forms. However, its applicability in non-Western populations such as Saudi Arabia has not been thoroughly investigated, and its reliability across various imaging techniques remains understudied.

While current research primarily focuses on clinical trials of new treatments targeting FD/MAS complications, such as bisphosphonates, denosumab, and surgical interventions, less attention has been given to advancing the diagnostic and assessment methods for skeletal involvement. Therefore, there is a critical need to explore the role of

SBS in assessing varying degrees of disease severity and its correlation with physical outcomes, as well as to ensure its reliability across clinicians from different specialities.

1.2 Aims

The main goal of this thesis is to evaluate the applicability of the SBS in assessing the extent of FD involvement in the skeleton. To achieve this goal, the thesis aims to:

- Assess the relationship between SBS and physical outcomes in FD/MAS patients.
- Investigate the level of agreement among multiple readers in applying SBS to bone scintigraphy and whole-body magnetic resonance imaging (WB-MRI) scans.

1.3 Thesis structure

This thesis was written and presented in the alternative thesis format, which is suitable for publication in peer-reviewed journals. The University of Sheffield supports this format, as it improves writing skills required for publication and encourages the PhD candidate to publish in a peer-reviewed journal.

This thesis is divided into two sections. Section 1 consists of **Chapters 2**, **3** and **4**, which are review chapters.

In details, **Chapter 2** provides a comprehensive review of the literature, beginning with basic bone biology and physiology, and progressing to the aetiology of FD/MAS. The chapter introduces a brief history of FD/MAS, detailing its description and its clinical complications, and concludes with the current international FD/MAS guidelines for the diagnosis, management and treatment plans.

Chapter 3 is a systematic review and meta-analysis titled, “What Is the Correlation Between Skeletal Burden Score and Functional Outcome in Patients with Fibrous Dysplasia? - A Systematic Review and Meta-Analysis”. This review aims to evaluate the relationship between the SBS and reported quality of life and physical outcomes.

Chapter 4 is another systematic review and meta-analysis titled, “The Diagnostic Accuracy of Cross-Sectional Imaging Modalities in Fibrous Dysplasia: A Systematic Review and Meta-analysis”. The aim of this review is to systematically investigate the sensitivity and specificity of the cross-sectional imaging modalities in the diagnosis of FD/MAS reported in the literature.

The primary aims of the thesis are addressed in Section 2, which comprises of **Chapters 5,6,7 and 8. Chapter 5** presents an effort to measure the clinician’s knowledge and use of the SBS through an online survey designed to assess this aspect. This chapter is developed and disseminated during the enforcement of COVID-19 pandemic restrictions, effectively utilising the time of my studies whilst working from home.

Chapter 6 titled “External Validation of the Skeletal Burden Score in Patients with Fibrous Dysplasia “. This chapter measures the intra- and inter-reader agreement of the use of SBS, derived from bone scintigraphy scans by five radiologists from the United Kingdom and Saudi Arabia. This chapter is currently under review by the Saudi Journal of Radiology.

Chapter 7, is the main study arm of this thesis, titled “The Assessment of the Quality of Life and the Skeletal Burden in Patients from Saudi Arabia with Fibrous Dysplasia “. This chapter presents a longitudinal study of FD/MAS patients from two collaborating sites in Saudi Arabia. The QoL, and bone pain are measured using validated questionnaires and

are compared to the QoL reported of FD/MAS patients from other countries. The study also, analyses the relationship between SBS with physical health aspects of QoL at baseline and at six months follow-up.

Chapter 8 presents a preliminary evaluation of the collaboration with Oxford University Hospitals, including FD/MAS patients registered in the Rare UK Diseases study (RUDY) registry. It involves the novel utilisation of SBS derived from WB-MRI. This chapter also assesses the inter-reliability of using SBS from WB-MRI and bone scintigraphy scans.

Finally, **Chapter 9** provides a summary of the findings from each chapter. The chapter discusses the overall strengths and challenges encountered during the PhD programme and outlines potential directions for future research.

Chapter 2: Literature Review

2.1 Basic bone biology

Bone is a complex living tissue of hierarchical structure that consists of minerals, organic components, and water, and its microstructure includes bone cells, and an extracellular bone matrix [1,2]. Bone cells account for 10% of bone volume and include osteoclasts, osteoblasts, and osteocytes. Osteoclasts are responsible for bone resorption and healing, whereas osteoblasts are bone-forming cells. Moreover, some osteoblasts differentiate into osteocytes during bone formation. Osteocytes, which are differentiated osteoblasts embedded within the bone matrix, act as a mechanosensors and play a crucial role in maintaining bone homeostasis by regulating bone remodelling and communicating with both osteoblasts and osteoclasts (Figure 2.1) [3,4].

The balance between osteoclasts and osteoblasts is important for a healthy musculoskeletal system. The extracellular bone matrix consists of an organic matrix, an inorganic matrix, lipids, and water [5]. The organic matrix, which makes up approximately 20% of the extracellular bone matrix, is secreted by osteoblasts and consists of type I collagen and non-collagen proteins. Type I collagen consists of a carboxy-terminal propeptide of type I procollagen (PICP), and an amino-terminal propeptide of type I procollagen (PINP). Non-collagen proteins, including glycoproteins, osteonectin, osteocalcin, osteopontin, proteoglycans, growth factors, and bone sialoprotein are proteins essential for processes such as bone matrix formation, mineral deposition, and the regulation of osteoblast and osteoclast activity. Inorganic bone matrices, such as phosphate, calcium, sodium, fluorite, magnesium, zinc, and others, provide the bone with rigidity and resistance to internal and external forces [6,7].

The bone macrostructure comprises two primary types: cortical and trabecular bone. Cortical or compact bone constitutes approximately 80% of the skeleton and forms a dense, thick outer layer, particularly in the diaphysis of long bones. Moreover, cortical bone is crucial for supporting, protecting, and facilitating mechanical functions [8]. Trabecular bone, also known as cancellous bone, accounts for approximately 20% of the skeleton and is in the inner layers of the bone [1,6]. It is less dense and more porous than cortical bone, because it contains higher degree of vascularisation, and houses red bone marrow, which is the site of haematopoiesis, blood cell formation, and osteocyte development. Trabecular bone is also more metabolically active than cortical bone and is the primary site of bone metabolism and remodelling.

The balance between the cortical and trabecular bone varies throughout the skeleton and changes over a person's lifetime as bone tissue continuously forms and remodels. This dynamic process includes growth, which increases bone size, and a complex procedure known as skeletal modelling, which is responsible for the evolved size and shape of the bones. During infancy, the skeleton consists of 270 bones; with ageing, and some bones fuse together to form 206 bones in adulthood [9].

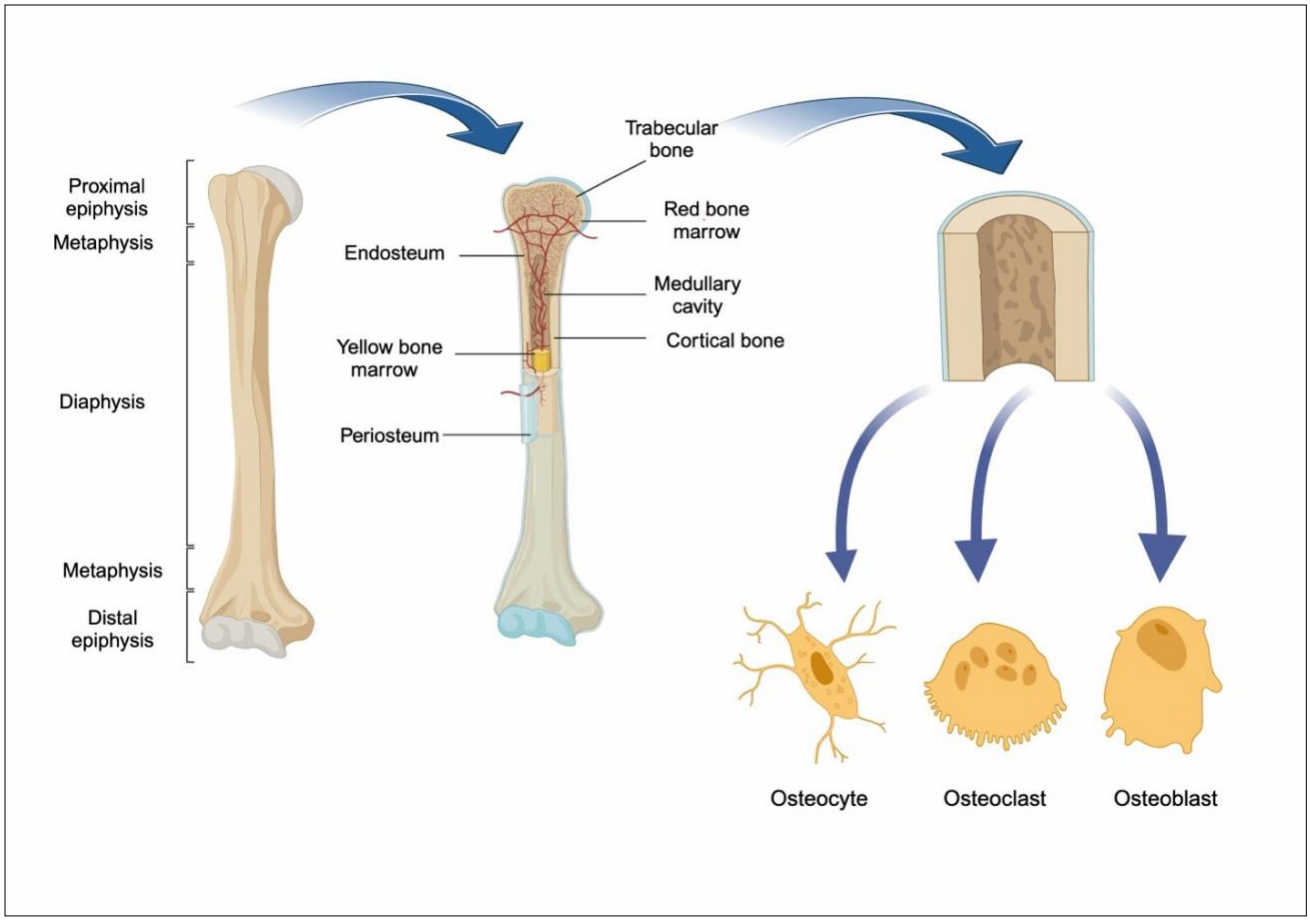

Figure 2.1 Basic bone components

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2.1.1 The skeleton

The skeleton is divided into two main parts: axial and appendicular skeleton [2]. The appendicular skeleton consists of 126 bones, which comprise the upper limbs, lower limbs, pectoral and pelvic girdles. The appendicular skeleton is essential for bearing weight, providing support, and enabling mobility and motion. The axial skeleton includes 80 bones consist of the skull, vertebral column, and the rib cage. The axial skeleton provides protection to vital organs such as the brain, lungs, heart, and spinal cord. Additionally, it supports the head and neck.

2.1.2 Bone physiology

2.1.2.1 Bone modelling

The formation of new bone, known as bone modelling, bears similarities to bone remodelling. However, a notable difference is that bone resorption and bone formation occur on separate occasions and are not coupled in the same locations. Moreover, bone modelling is a rapid and continuous process that can involve either the removal of old bone or the creation of new bone tissue, but not the replacement of existing or old bone. Bone formation markers, including alkaline phosphatase (ALP), osteocalcin, and the (PINP), are indicators of osteoid production by osteoblasts. These markers are crucial for assessing the rates of bone metabolism and remodelling.

Bone turnover markers (BTMs) for bone formation include osteocalcin, ALP, PINP, and the PICP. BTMs are of two types: bone formation and bone resorption markers.

Numerous factors can influence bone modelling, such as hormonal balance, physical activity, and nutrition. Increases in physical activity, especially weightlifting, activate bone modelling. Furthermore, mineral intake, such as calcium and magnesium, is important for bone growth [4] . The balance between bone modelling and remodelling is important, and any abnormal imbalance between them can lead to bone disorders. For instance, osteoporosis is linked to excessive bone resorption, resulting in fragile bones with low density and a high risk of fractures and bone pain [4].

2.1.2.2 Bone remodelling

The cyclical process of bone remodelling that maintains skeletal integrity by repairing damaged bones, replacing old bone, and regulating plasma calcium homeostasis [10]. At the cellular level, bone remodelling is divided into four main phases: activation and resorption phases, where osteoclasts initiate the resorption of old and damaged bone; the reversal phase, where osteoclasts undergo apoptosis and osteoblasts are initiated for bone formation; and the formation phase, where osteoblasts secrete organic bone matrix to form new bone [7,11]. Bone resorption markers are byproducts of osteoclasts formed during the resorption phase, including serum C-telopeptide of type I collagen, urinary N-telopeptides of type I collagen, and tartrate-resistant acid phosphatase [7].

Bone remodelling is more frequent on the trabecular bone surface than within cortical bone. However, bone remodelling does occur in Haversian canals in cortical bone [12]. Several hormones significantly influence bone remodelling, Parathyroid hormone (PTH) and vitamin D play crucial roles in calcium homeostasis and bone resorption regulation. Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) promote bone growth by

enhancing osteoblast activity. Oestrogen and testosterone protect bone by reducing resorption and increasing formation [4,13].

The pace of bone resorption and formation changes with age; in children, formation exceeds resorption, resulting in denser and heavier bones. In young adults, the pace of bone resorption and formation processes are balanced, maintaining bone mass. In older adults, resorption surpasses formation, leading to bone loss and increased fragility. These changes are influenced by the natural timeline of skeletal growth and hormonal fluctuations throughout life.

2.1.2.3 Bone growth

Bone growth alters the shape and size of the bone, depending on the type and location of the bone. The modelling process is highly active during the peak of bone mass. Intramembranous and endochondral bone formations are types of bone modelling [1]. Intramembranous bone formation occurs in the skull, pelvic bones, and craniofacial bones, while endochondral bone formation takes place in long bones. Both processes occur during embryogenesis.

There are two types of bone growth: longitudinal and appositional. Longitudinal bone growth occurs at the epiphyseal plate of the cartilages in childhood and adolescence. After adolescence, the epiphyseal plate ossifies, and the epiphysis and the diaphysis fuse together, leading to a gradual cessation of bone growth in the early years of adulthood. On the other hand, appositional bone growth, which increases the diameter of the bone and cortical bone thickness, is a continuous process triggered by physical activity and stress response [10].

2.2 Fibrous dysplasia

Fibrous dysplasia (FD) is a rare, non-inherited, mosaic bone disorder, accounting for approximately 5% of benign bone tumours [14,15]. It is characterised by the replacement of normal bone with abnormal fibrous tissue, consisting of a mixture of immature osteoblasts, osteocytes, irregular and immature trabecular cells, resulting an abnormal bone composition and structure [16-19]. In 1891, FD was first reported by Von Recklinghausen, who observed bone deformity and abnormal fibrous tissue in two cases of hyperparathyroidism, and termed this condition *"osteitis fibrosa generalisata"* [20]. For many years, FD was considered secondary to hyperparathyroidism. In 1931, Turnbull noted that not all FD cases were associated with parathyroid abnormalities, FD lesions were localised, and other parts of the skeleton were normal. Turnbull named this lesion osteitis fibrosa. Later, in 1937, McCune, Bruch, and Albright documented the association of multiple FD lesions with café-au-lait pigmentation, and precocious puberty, which was described and titled "Albright's brown-spot syndrome," now known as McCune-Albright syndrome (MAS) [21].

The following year, Lichtenstein described the clinical characteristics of FD in eight cases and introduced the term “fibrous dysplasia of bone” [20,22]. Lichtenstein and Jaffe later reported further cases with a more detailed observation of FD clinical complications and documentation of FD subtypes. In 1954, Belaval and Schneider introduced a classification of FD as follows: Type 1 refers to monostotic FD, Type 2 to polyostotic FD, and Type 3 to disseminated FD lesions with the presence of extra skeletal manifestations [23]. In 2019, an international consortium of world-clinician experts on FD/MAS gathered and established a detailed description of FD aetiology, complications, diagnosis, treatment of clinical complications, and management plans [24].

2.2.1 The etiology of FD

Fibrous dysplasia is caused by missense somatic mutations of the α subunit of the stimulatory G protein (*GNAS*) gene on chromosome *20q13*, leading to the overproduction of cyclic adenosine monophosphate (cAMP). As a result of constitutive cAMP production, the normal bone marrow stromal cells (BMSCs) are inhibited from differentiating into osteoblasts, adipocytes, and haematopoiesis-supporting stroma [2527]. Consequently, the failure of bone remodelling caused by proliferated BMSCs creates abnormal fibrous tissues, leading to a wide range of clinical complications, such as pathological fractures, bone pain, deformity, progressive scoliosis, malignant transformation, and functional impairment [28,29]. The FD incidence rate is between 1:4,000 to 1:10,000 equally between male and female [30][20] [31]. The mosaic nature of FD results in a wide clinical spectrum, from asymptomatic, isolated single lesion (monostotic FD) to multiple FD lesions (polyostotic FD) accompanied by extra-skeletal manifestations causing functional

disabilities. The relationship between FD severity and the timing of *GNAS* mutations during the osteogenesis phase is correlated; early mutation of the *GNAS* gene is associated with severe FD involvement, such as polyostotic FD or MAS, while late *GNAS* mutation is associated less FD involvement such as monostotic FD [28]. FD lesions can occur anywhere in the skeleton, with a preference for the femur, tibia, craniofacial bones, pelvis, and ribs [19]. FD lesions in the appendicular skeleton have a higher rate of clinical complications, such as bone pain and pathological fractures, due to weight-bearing forces on the lower extremities [32,33]. Furthermore, FD involvement of the craniofacial bones has been reported to cause expansion, leading to bone deformities and the compression of the optic nerves and the auditory canals [34-37].

2.2.1.1 Progression of FD

The status of FD metabolic activity is driven by ageing and natural bone growth (Figure 2.2). In utero, early and late GNAS mutations take place without obvious FD symptoms at birth. Moreover, by the age of five years, most FD lesions can be detected by radiological imaging, especially those in the craniofacial bones. Between the ages of 10 and 15 years, most clinical complications of polyostotic FD and MAS appear. The status of FD metabolic activity remains active until bone growth reaches its peak, at which point the FD skeletal burden is established. In adulthood, FD lesions become metabolically inactive, which is called the “burn-out” phase. Natural bone density changes are associated with an increased risk of bone fractures and pain [16,31].

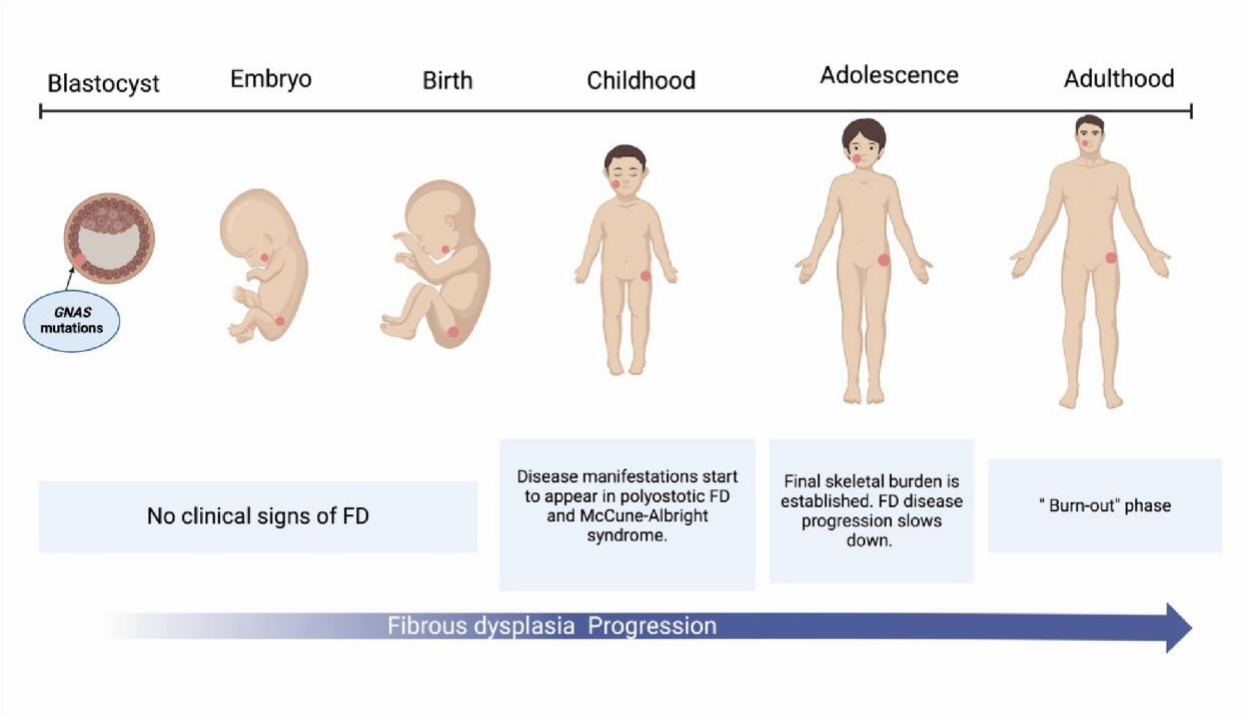

Figure 2.2 Fibrous dysplasia progression
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2.2.1.2 Monostotic fibrous dysplasia

The most common FD subtype is monostotic FD, which accounts for 60-75% of all FD cases [19]. Monostotic FD lesions are frequently asymptomatic and found incidentally on diagnostic imaging as part of an investigation of unrelated abnormalities. The most common sites for monostotic FD lesions are the craniofacial bones, ribs, femur, tibia, and lastly, the humerus [16]. Complications arise from monostotic FD typically occur between the ages of 20 and 30. The most reported clinical complaints that arise from monostotic FD are bone pain and pathological fractures [19].

2.2.1.3 Polyostotic fibrous dysplasia

About 20% to 30% of FD cases are polyostotic FD [16]. Polyostotic FD complications such as progressive scoliosis, bone pain, and pathological fractures typically begin in childhood, earlier than monostotic FD [24]. Polyostotic FD, usually occurs unilaterally and can affect various bones, including the femur, the tibia, craniofacial bone, pelvis, ribs, humerus, radius, and spine.

2.2.1.4 McCune–Albright syndrome

McCune-Albright syndrome accounts for 2% to 3% of polyostotic FD, with a prevalence ranging from 1 in 100,000 to 1 in 1000,000 [14.31]. Initially, MAS was described as a triad of polyostotic FD, café-au-lait skin macules, and precocious puberty [20]. It was later found that MAS involves endocrine and non-endocrine extra-skeletal manifestations, depending on where *GNAS* mutations occur, which can be in a tissue, organ or organ system [38].

Table 2.1 summarises the extra-skeletal manifestations of MAS. Precocious puberty is the most common endocrinopathy, affecting 80% of MAS patients, with females being more frequently affected by precocious puberty than males, and symptoms manifesting at a very young age [14,31]. In females, early symptoms of precocious puberty include vaginal bleeding, breast enlargement, and rapid growth. In boys, early symptoms of precocious puberty include enlarged testicles, facial hair, and rapid growth [38]. About 50% of MAS patients are diagnosed with hyperthyroidism, which is caused by the increased conversion of thyroxine (T4) to triiodothyronine (T3) leading to T3 hormone excess. Another endocrinopathy associated with MAS is GH excess, with a prevalence of 20%, and affecting males greater than females. Symptoms of excessive secretion of GH appear before the age of 20, with tall stature is being the most common symptom [39]. Excess secretion of GH with FD involvement of the craniofacial is linked with macrocephaly and vision and hearing loss [38].

Other less prevalence endocrine manifestations are hyperprolactinemia, hypercortisolism (Cushing's syndrome) [31,24]. The most common non-endocrine abnormalities are café-au-lait macules, characterised by irregular, rough borders (often described as resembling 'the coast of Maine') and present from birth [40]. Cafe-au-lait spots typically appear on the body's midline, on the same side as the FD lesion [16,28,41]. About 50% of MAS patients have renal phosphate wasting, due to mutations of *GNAS* activated in the kidney. Excessive fibroblast growth factor-23 (FGF-23) secretion causes renal phosphate wasting, resulting in low phosphorus serum levels, abnormal renal reabsorption, and inadequate bone mineralisation.

FGF-23 is a phosphaturic, bone derived hormone that plays a crucial role in regulating renal phosphate excretion and vitamin D synthesis. Other non-endocrine manifestations include cardiac disease, hepatobiliary dysfunctions, and gastrointestinal diseases, which are rare but reported in the literature [14,31,38].

Table 2.1 Extra-skeletal manifestations of McCune-Albright syndrome

Endocrine manifestations
Precocious puberty
Hyperthyroidism
Excess of Growth hormone
Excess of prolactin hormone
Hypercortisolism (Cushing's syndrome)
Non-endocrine manifestations
Café-au-lait skin pigmentations
Renal phosphate wasting
Cardiac disease
Hepatobiliary dysfunction
Gastrointestinal diseases

2.2.1.5 Mazabraud's syndrome

The rarest FD form is Mazabraud's syndrome, accounting for approximately 1% to 3% of all FD cases [19], with a 2.4% increase in prevalence reported in a recent study [4242]. Mazabraud's syndrome is characterised by intramuscular myxoma, a benign neoplasm manifesting as either a single or multiple soft tissue tumours located in the same region as the FD/MAS lesion. The intramuscular myxoma was first described in 1926 by Henchen et al. [43].

In 1967, Mazabraud et al. identified the intramuscular myxoma association with FD and subsequently named the condition Mazabraud's syndrome [44]. Mazabraud's syndrome is predominantly linked with polyostotic FD; however, in rare cases, it can coexist with monostotic FD and MAS. Reports often highlight the syndrome's association with MAS, including café-au-lait spots and endocrinopathies [45]. Females are more frequently affected by Mazabraud's syndrome than males. Pain is the most common reported symptom of Mazabraud's syndrome. Myxomas are most common in the lower extremities, particularly the thigh muscles, followed by the shoulders and buttocks. Mazabraud's syndrome presents a higher risk of malignant transformation compared to FD/MAS without the presence of intramuscular myxoma [46].

2.2.2 Clinical complications

2.2.2.1 Bone pain

The most reported complication of FD is bone pain, which significantly impacts the quality of life (QoL) [47]. Bone pain is categorised into two main types: nociceptive pain, which is acute pain caused by external stimuli resulting in tissue damage, and neuropathic pain, which is chronic pain caused by an abnormality or condition that results in nerve damage. Pain experienced can be a combination of both nociceptive and neuropathic pain. In FD/MAS, bone pain can manifest as either nociceptive or neuropathic, each with its own targeted treatments. A retrospective study of two large online registries: the Fibrous Dysplasia Foundation (FDF), and the Rare UK Diseases Study (RUDY) analysed the reported bone pain in 249 FD/MAS patients [48]. Spencer et al. used the painDETECT questionnaire to measure pain intensity, identify pain location and determine the type of pain. Neuropathic pain was reported more frequently than nociceptive pain, especially in female participants. In addition, neuropathic pain was associated with impaired QoL, poor sleep quality, depression, and anxiety. Differences in pain prevalence between sexes are also notable, with females generally reporting more pain than males, regardless of similar severity levels. This discrepancy may be attributed to a higher prevalence of chronic conditions in females or inherent differences in pain sensitivity and tolerance [49].

The location of FD involvement is linked to the intensity of the associated pain. An observational study of FD/MAS patients assessed pain in 78 children and adults diagnosed with FD/MAS using the brief pain inventory (BPI) questionnaire [50]. Kelly et al. reported greater pain intensity associated with FD of the lower extremities and

craniofacial bones. These findings aligned with Majoor et al. [51], who assessed bone pain in 197 FD/MAS adult patients using the pain numeric rating scale questionnaire. Adults with FD/MAS reported greater pain intensity pain compared with children [51]. However, this difference does not diminish the occurrence of bone pain in younger populations but highlights the challenges in assessing pain in children [50]. Another possible reason could be related to changes in bone density, which contribute to less dense bones and an increased risk of fractures, potentially elevating pain experiences in adults [51,52].

2.2.2.2 Pathological fractures

Hypophosphatemia significantly impacts bone density, leading to intrinsic osteomalacia, and subsequently, a higher rate of fractures in the FD lesion areas. The prevalence of hypophosphatemia is not dependent on age but is notably higher during periods of bone growth [53]. A retrospective study involving 172 patients diagnosed with polyostotic FD across various age groups revealed a strong correlation between increased phosphaturia and an elevated rate of fractures. The highest rate of fractures was observed in children between the ages of 6 and 10 years, with a noticeable decline during adolescence and early adulthood. Remarkably, a second peak in fracture rates was identified in patients older than 36 years, corresponding to the natural decline in bone density [54]. Pathological fractures, particularly of the lower extremities, are prevalent due to the natural weight-bearing forces exerted on the long bones, leading to physical disability and often necessitating the use of ambulatory devices (crutches, canes and wheelchair) [47] [55,56].

2.2.2.3 Bone deformity

The natural expansion of FD lesions leads to weakened bones, eventually causing bone deformity and fractures [16]. Complications arises from bone deformity, including the compression of vital organs such as nerves, the brain, eyes, lungs and heart, further causing restriction or compression of these organs. Shepherd's crook deformity, characterised by the bowing of the proximal femur, is a common manifestation of polyostotic FD in the long bones [14,15]. Another common FD deformity is scoliosis, affecting 40% of patients with spinal involvement. Patients with polyostotic FD/MAS are more likely to experience spinal involvement compared to those with monostotic FD [57]. A retrospective study by Berglund et al. [58] evaluated the prevalence and severity of scoliosis in a large FD/MAS patient cohort, reporting an 81% prevalence of scoliosis. The severity of scoliosis was measured using the Cobb angle and was categorised as mild (10 – 30 degrees), moderate (30 to 45 degrees), and severe (> 45 degrees). Notably, scoliosis was found to be associated with hypophosphatemia and hyperthyroidism (p-value <0.001 for both). Scoliosis was also caused by leg length discrepancies, pathological fractures, bone pain, and progressive disability.

2.2.2.4 Malignant transformation

The incidence of malignant transformation in FD cases is rare, with a reported rate of 1% across all FD cases, with no significant difference observed between sexes [59]. However, the likelihood of malignant transformation is heightened in cases of polyostotic FD and MAS compared to monostotic FD [19,60]. The mortality rate of malignant transformation is about 53.6% in FD patients [59]. The cause of FD malignant transformation is unknown, but it might be related to external radiation exposure, such as radiation therapy, is considered a potential contributing factor [15,19,59]. The exact mechanism driving the transition from benign fibrous tissue to malignant osseous sarcomatous lesions remains unclear. Malignant transformation tends to occur in adulthood, marked by sudden and rapid growth of the FD lesions, causing swelling, bone deformity and pain often without preceding trauma [60]. The most frequent sites for malignant transformation include the skull, mandibular bones, femur, and tibia [19]. Osteosarcoma is the most common type of malignancy secondary to FD/MAS, followed by fibrosarcoma, chondrosarcoma, angiosarcoma and spindle cell sarcoma [17].

2.3 The diagnosis of fibrous dysplasia

The evaluation and staging of FD/MAS include clinical tests, radiological imaging, histopathological analysis, and genetic analysis of GNAS mutations. As outlined in the international FD/MAS guidelines [61], a comprehensive clinical, histopathological, and radiological assessment of the FD skeletal and extra-skeletal manifestations are crucial for distinguishing FD from other conditions with similar presentations, such as benign and malignant bone tumours.

2.3.1 Clinical testing

The measurement of BTMs, thyroid function, PTH, renal functions and basic biochemistry such as vitamin D, calcium, phosphate is essential to evaluate endocrine and metabolic bone functions [24]. BTMs are indicative of the slow bone remodelling, and insufficient mineralisation characteristic of FD/MAS, causing elevated levels of BTMs. It is natural for BTM levels to be high in childhood, with a gradual decrease through adolescence into adulthood [62]. Commonly measured BTMs include ALP, P1NP, and C-terminal telopeptide (CTX), which can be measured via blood or urine sample. The international FD/MAS guidelines consider the measurement of ALP as the minimum requirement to assess metabolic activity [24]. of Measuring BTMs can provide insights into the metabolic activity of FD/MAS, and the efficacy of treatment; however, the interpretation of these markers much be with caution [24]. Moreover, BTMs are markedly influenced by factors such as age-changes, hormones, sex, and the use of treatments for bone pain [62]. Therefore, the clinical measurement of BTMs should be corroborated with radiological, histopathological or genetic confirmation of the FD/MAS disease.

2.3.2 Histological assessment

Bone biopsy is a surgical procedure for extracting a sample from the abnormal lesion for tissue analysis. However, bone biopsies are generally reserved for monostotic FD due to the impracticality of sampling multiple lesions in polyostotic FD [63,64]. Under microscopic examination, the FD histological features are classical with yellow-white, delicate immature trabeculae of woven bone that resemble 'alphabetic soup' or 'Chinese letters [14]. Despite the diagnostic value of bone biopsies, they represent a high risk of false negatives, as the sample may contain normal bone cells, and the biopsy may need to be repeated [65]. Another negative of bone biopsy, in which the extraction of a sample might damage the nearby nerve or blood vessels [25]. Histopathological testing is the standard diagnostic method of confirming FD/MAS in monostotic FD (especially those affecting craniofacial bones or areas with overlapping anatomical features) and when suspecting malignant transformation of FD [24,61].

2.3.3 Genetic testing

The detection of the *GNAS* mutations can be undertaken through polymerase chain reaction (PCR) analysis of the DNA sequences from FD lesions or by employing next generation sequencing (NGS), or Sanger sequencing [63]. PCR has superior sensitivity of 80% compared to other genetic sequencing methods [31]. Genetic testing of the FD/MAS also plays a crucial role in distinguishing FD lesions from other malignant lesions, such as fibromas in craniofacial bones, thereby aiding in the accurate diagnosis and management of these conditions.

However, negative genetic sequence doesn't rule out FD/MAS, thus the finding should be confirmed by histopathological or radiological confirmation of FD/MAS disease [66].

2.3.4 Radiological imaging

Radiological imaging is an important diagnostic tool in FD/MAS, offering insight into the lesion's characteristics and the overall extent of disease involvement. Conventional plain radiography, often the initial step in imaging when FD is suspected, helps in differentiating FD lesions from other abnormalities. Computed tomography (CT) and magnetic resonance imaging (MRI) which both provide in-depth morphological details about the FD lesion and the adjacent soft and muscle tissues. Also, CT and MRI offering crucial information on areas such as a craniofacial and spinal bones that might be missed on radiographs. Nuclear medicine imaging is used to assess the skeletal extent of FD, and evaluate the metabolic activity of the lesions, which is contributory in understanding the FD/MAS involvement and progression. Table 2.2 summarise the FD features of each imaging modality.

Table 2.2 Summary of imaging modalities in the diagnosis of fibrous dysplasia

Imaging modalities	FD features	Limitations	Utility
Conventional Radiography	• Varies depending on the location of FD involvement and amount of fibrous tissue. Generally, FD lesion is poorly defined, expansile FD lesion. • The radiological appearance of FD lesion can sclerotic or cystic or mixture of both. • Craniofacial FD have classical ground glass appearance.	• Cannot differentiate between FD and other bone tumours. • FD appearance varies depending on the bone involved, amount of mineralisation within the lesion, and FD progression.	First line of assessment FD.
Computed Tomography	• Ground glass appearance, homogenous pattern, with sclerotic rim. • CT density measurements of FD between 70-130 HU. Lesion enhancement after intravenous contrast administration.	Exposure to Ionising radiation.	• Golden standard for craniofacial imaging. • Assessment of nerve compression, deformity, FD progression changes, malignant transformation. • FD lesion density measurement.
Magnetic Resonance Imaging	• Varies depending on the amount of calcifications, collagen and cystic changes. Intermediate to low intensity on T1-WI. • Intermediate to high intensity on T2-WI, few trabeculae the lower T2-WI signal.	• Non-specific FD characteristics. • The need for sedation when imaging children.	• MRI is complementary to CT. No ionising radiation involved. • Diffusion- weighted imaging to differentiate benign to malignant tumours.
Nuclear Medicine	• Significant radionuclide uptake within FD lesion. • Foci uptake of the metabolically active FD lesions.	• Non-specific FD appearance. • Exposure to Ionising radiation.	• Ideal when suspecting polyostotic FD. • Evaluate FD involvement as young as five years. • ^{99m}Tc-MDP is as skeletal survey. • Semiquantitative data of FD involvement using ^{18}F-FDG and ^{18}F-NaF PET/CT.

Abbreviations; CT, computed tomography; FD, fibrous dysplasia; 18F-FDG, F-18 fluorodeoxyglucose; ^{18}F-NaF, ^{18}F, sodium fluoride; HU; PET/CT; ^{99m}Tc-MDP, ^{99m}Tc-methylene diphosphonate

2.3.5 Radiological features of fibrous dysplasia lesions

2.3.5.1 Conventional radiography

The radiographical characteristics of FD lesions, vary significantly based on the amount of osseous tissue and the type of bone affected [17]. Lesions of FD can appear cystic, sclerotic, or mixture of both appearances. Radiographically, FD lesions exhibit expansion from the medullary cavity to the cortex, with thinning of the cortical bone surrounding the lesion. This classical appearance of FD is often described as ‘ground glass’, radiopaque pattern with ill-defined borders of FD lesion blended with the surrounding normal tissue [17,29]. The radiological appearance of craniofacial FD lesions also varies depending on the maturity of the FD lesion; new, immature FD lesions appear more heterogenous and radiolucent (cystic); while older, mature FD lesions are more homogenous and present with ground glass appearance. Pelvic and ribs bones have expansile, lytic radiological appearance [14] [24]. The presence of pathological fractures changes the appearance of the cortex, resulting in a sclerotic appearance of FD under radiographs [16]. In addition, the presence of cartilage tissue within the lesions may lead to calcification findings on radiographs [67].

2.3.5.2 Computed tomography

The classical ground-glass appearance, a hallmark of FD lesion is present in both radiographs and CT scans. CT is considered the gold standard for assessing craniofacial and monostotic FD lesions [68,69], [56], suspicions of malignant transformation, and cases of nerve compression [24,69]. Although, radiographs and CT scans may present similar radiological features of FD, radiographs fall short in distinguishing FD from other benign bone tumours, such as osteomyelitis and neoplasms [70]. CT is superior in providing detailed density measurements which are pivotal for differentiating FD from other abnormalities. These measurements are given in Hounsfield units (HU), with FD lesion shown a density range from 70 to 130 HU, contrasting with lower HU values of 20 to 40 in osteomyelitis [71].

Adjusting the CT window is a technique of changing contrast and brightness post imaging, to aid in differentiation of FD lesions from malignancies and other benign tumours [16]. The CT bone window setting enhances the visualisation of bone expansion and opacification ranges [72], while the soft tissue window setting allows for visualisation of the involved soft tissue within the FD lesions. CT imaging is useful for investigating craniofacial FD, especially in complex and detailed structures such as the orbits, and maxilla [68]. Three-dimensional reconstructive helical CT offers better resolution and visualisation of the craniofacial bone structures (e.g. optic canal) compared to two-dimensional CT imaging [72,73].

2.3.5.3 Magnetic resonance imaging

The radiological features of FD lesions under MRI are non-specific on T1- , and T2-weighted images influenced by factors such as the amount of bone trabeculae, calcifications, level of cellularity, cystic changes, amount of collagen, and haemorrhagic changes [68]. Increased cystic changes within the FD lesion is linked with high signal intensity on T2-weighted images, whereas increased in bony trabeculae is linked with low signal intensity on T2-weighted images [68]. Metabolically inactive FD lesions generally exhibit intermediate-to-low signal intensity on T1-weighted images, whereas active FD lesions exhibit high-to-intermediate signal intensity on T2-weighted images [16,68]. Moreover, the amount of cartilage and collagen on the FD lesion demonstrated low to intermediate signal intensity T1-weighted images, and intermediate to high signal intensity on T2-weighted images [74]. Differentiating metabolically active from nonactive FD lesion can be by evaluating post-contrast enhancement; active FD lesion demonstrated avid enhancement and while inactive FD lesion showed milder enhancement [69]. FD lesions exhibit a black rim called rind which is seen in post contrast enhancement on T1- and T2- weighted images MRI [75,76].

Diffusion-weighted imaging (DWI) is MRI technique which is superior to conventional MRI in the assessment of fluid-filled cystic lesions by measuring the apparent diffusion coefficient (ADC) [77]. The ADC values were computed automatically using image processing software and presented as $10^{-3}mm^2/s$. Two studies demonstrated high ADC values of $2x10^{-3}mm^2/s$ of FD lesion in the skull compared to other benign and malignant brain tumours [78,79]. MRI is useful in the investigation of suspected malignant transformation and nerve compression within detailed anatomical structures, such as the skull and the spine. Its capacity to assess the impact of FD lesions on surrounding connective and muscle tissues further underscores its utility. Importantly, MRI is highly recommended for use in children, given its non-invasive nature and the absence of radiation exposure, which makes it a safer alternative compared to other imaging modalities [16,61]. However, the requirement for sedation in paediatric imaging is a notable drawback of MRI. Moreover, the non-specific and variable signal intensity of FD lesions on MRI indicates that MRI should not be used as the sole diagnostic tool. Instead, it is recommended as a second-line imaging modality for FD assessment and monitoring disease progression [69].

2.3.5.4 Nuclear medicine imaging

Nuclear medicine imaging exclusively captures the physiological features of FD involvement, differentiating between metabolically active and inactive FD lesions. According to the international FD/MAS guidelines, bone scintigraphy is recommended when suspecting polyostotic FD and in staging the extent of FD involvement in the skeleton by the age of five [61]. Planar bone scintigraphy employs ^{99m}Tc-methyl diphosphonate (MDP) or hydroxyl diphosphonate (HDP). The sensitivity of ^{99m}TcMDP/HDP is considered high, but specificity is limited due to normal distribution of 99mTc-MDP/HDP in the skeleton. Kidneys, and the bladder [80].

Metabolically active FD lesions show intense uptake of ^{99m}Tc-MDP /HDP, correlating with proliferation rates of BTM or FGF-23 in the lesions [31]. According to the EANM guidelines, the ^{99m}Tc-MDP /HDP administered dose typically receive 300-740 MBq (8-20 mCi) for adults, and 40375 MBq (1-10 mCi) for children [81]. Three-phase bone scans, taken two to four hours post-tracer administration, evaluate the tracer uptake in three phases: flow, blood pool, and delayed, revealing increased blood flow and uptake in immature woven bones during the delayed phase [82]. Single photon emission computed tomography (SPECT) enhances diagnostic imaging with greater specificity over planar gamma camera, offering dynamic 360 degrees capabilities. Integrated with CT, SPECT/CT merges physiological details from SPECT with anatomical details from the low dose CT, improving high sensitivity and specificity of identifying abnormalities [83]. However, the use of SPECT/CT is constrained by its availability and cost, making it less accessible than the more economical planar gamma camera [84].

Positron emission tomography (PET) imaging is a three-dimensional imaging modality, with superior sensitivity in detecting metabolic activity and the assessment of disease progression compared to SPECT. The common radiotracer used for PET imaging, emits positron such as fluorine-18 (^{18}F). The fusion of PET with CT or MRI to provide an accurate anatomical detailed information combined with PET in same image. PET imaging provides semiquantitative data of the radiotracer uptake. Standardised uptake value (SUV) measures the glucose metabolism within certain area using a specific formula. Region of interest (ROI) the relation of the injected dose to the weight of the patient. Volume of interest (VOI) of the target area [83]. The most common PET scan used in diagnosing FD/MAS, 18-F-fluorodeoxyglucose (^{18}F-FDG) and 18-F-sodium fluoride (^{18}F-NaF) whole body scans [83, 85, 86]. According to EANM guidelines, the ^{18}FNaF administration dose of 1.5-3.7 MBq/kg (0.04- 0.1 mCi/kg) for adults, and 2.2 MBq/kg (0.06 mCi/kg) for children [87].

2.3.6 Radiation exposure and malignant transformation

The effective radiation dose, measured in millisieverts (mSv), reflects the amount of radiation absorbed by organs for each scan [88]. Radiation dose varies based on the organ being scanned, the imaging modality, and the imaging protocol and parameters. Table 2.3 summarises the effective dose measured for each imaging modalities [89].

Frequent repeated imaging for monitoring the progression of FD/MAS, treatment responses and surgical outcomes, which cumulatively expose the patients to higher cumulative radiation exposure [90]. Moreover, the transformation of FD lesions into malignancies has been linked to radiation exposure from radiation therapy or repeated imaging scans. The benefit of medical imaging outweighs the risks; however, unnecessary ionising radiation exposure is crucial and the use of alternative nonionizing medical imaging such as MRI is recommended for treatment and disease progression follow-up [61,68].

Table 2.3 Effective radiation dose of different imaging modalities

Imaging modality	Organ	Average effective dose (mSv)
Conventional Radiograph	Skull	0.1
	Spine	0.6
	Pelvis	0.2 - 1.5
Computed tomography	Skull	2
	Spine	6
	Pelvis	6
Bone scintigraphy (^{99m}Tc-MDP)	Whole-body	4.2 - 6.3
Positron Emission Tomography (^{18}F-FDG)	Whole-body	2.52 - 6.216

All the effective doses are measured for adults.

2.4 Treatment and management of the disease

Currently, no treatment exists that can cure or prevent FD/MAS. The international FD/MAS guidelines recommend the focus on optimising functional abilities and managing complications associated with FD/MAS [61]. Treatment can include bone pain relief and the surgical correction or the removal of the lesion.

2.4.1 Medications

Bone pain relief is challenging in FD/MAS, due to the variation of pain intensity which causes underestimation of the pain impact on the patients. Paracetamol is first line treatment for mild to moderate pain. If found no relief, the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen is recommended. A stronger analgesic such as opioids should be considered with cautions [61]. Although there is no treatment capable of altering FD/MAS, the use of bisphosphonates and other antiresorptive treatments has been proven to have a positive impact on the clinical complications arising from FD/MAS in minimising pain and sometimes the expansion of active FD lesions.

Bisphosphonate is the most common FD/MAS antiresorptive treatment. It is effective for treating bone pain and preventing further FD lesion expansion and thereby reducing the chances of pathological fractures. The mechanism of bisphosphonate treatment is that it increases bone density and reduces bone turnover [61, 91]. Chapurlat et al. [92], evaluated the pain in FD/MAS patient cohort at baseline and after six months of intravenous administration of pamidronate treatment. Approximately 40% of the patient cohort reported a reduction in bone pain, 18% had a reduction in ALP levels, and 20%

had a reduction in serum osteocalcin. Furthermore, 50% of the cohort had improvement in FD lesions on radiographs following pamidronate treatment.

According to the international FD/MAS guidelines [61], to maximise the benefits and minimise the side effects of bisphosphonate treatment, calcium and vitamin D levels should be maintained within the normal limits, and renal phosphate wasting should be treated for at least six months prior to starting treatment. Another medication that has a similar effect to bisphosphate is denosumab, a monoclonal antibody to the receptor activators of nuclear kappa-B ligand (RANKL/RANK) expression. This medication increases bone resorption. Denosumab was reported to inhibit lesion growth and reduce bone pain in a child with rapid FD lesion expansion. The unpleasant side effects of denosumab are hyperparathyroidism and hypophosphatemia [15].

2.4.2 Surgical treatment

Surgical treatment and corrections for FD/MAS are challenging as they rely on many factors, such as the activity of the FD lesion, the location of the lesion, the presence of weight-bearing forces, the associated clinical symptoms, such as bone pain, recurrent pathological fractures, and partial or complete physical disability. Internal fixation, such as with intramedullary devices, is the most common surgical procedure in FD of the lower extremities. The surgical correction of scoliosis involves surgical fusion and bracing by aligning the spine [93]. Another surgical approach is the removal of solitary FD lesion such as the removal of myxomas in Mazabraud's syndrome, monostotic, and craniofacial FD lesions [45,56].

2.5 The management of fibrous dysplasia

Figure 2.3 highlights the key elements of the FD management plan. Managing FD complications is particularly challenging due to the wide clinical spectrum of the disease, which necessitates a multidisciplinary approach involving clinicians from various specialities.

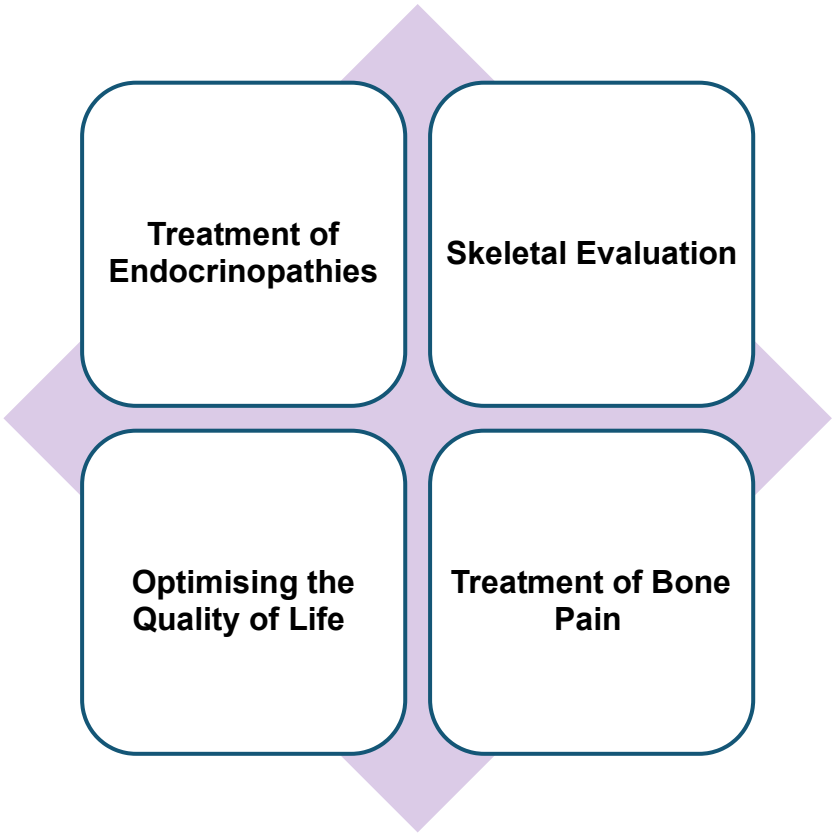


Figure 2.3 Elements of fibrous dysplasia management.

2.5.1 Treating Endocrinopathies

In MAS, the treatment of endocrinopathies targeted the affected hormone. Treatment of precocious puberty is an important to prevent premature maturation and other complications in children. Treatment for precocious puberty is different between girls and boys, consisting of the aromatase inhibitor letrozole in girls, and testosterone blockers in boys [31]. Excess growth hormone is linked with risk of craniofacial morbidity. Vision loss, nerve compression, and macrocephaly can be treated with intravenous octreotide to control growth hormone excess [94]. For hyperthyroidism, treatment can be anti-thyroidal medications, radioiodine therapy and in uncontrolled cases thyroidectomy [95]. The treatment of FGF-23 excess depends on the cause of such excess In FD the treatment of FGF-32 excess is oral phosphorus [96].

2.5.2 Optimising physical functions and the quality of life

The assessment of the QoL provides an overview of the individual's physical and mental health. In clinical practice, QoL questionnaires measure the impact of the disease on the patient's QoL and can be used to assess treatment outcomes [97]. To the best of our knowledge, there is no FD-specific QoL assessment tools; thus, previous studies have used generic QoL questionnaires. The majority of the generic QoL assessment questionnaires designed to cover physical, mental, and general health. The international FD/MAS guidelines recommend the use of generic QoL instruments such as 36-item short survey (SF-36), and the EuroQoL-5Dimension (EQ-5D-5L) for adults and paediatric quality of life (Peds-QL) in children [24].

Many studies have evaluated the quality of life of FD/MAS patients in relation to different reference standards. The impact of FD/MAS on the QoL is notably negative, particularly concerning physical health. However, FD does not appear to significantly impact mental health, as it remains comparable to the reference standard [41,47,55].

2.5.3 Assessment of bone pain

The assessment of bone pain to understand the level of pain intensity and interference with performing daily activity [24]. The Brief Pain Inventory (BPI) is a validated self-reported questionnaire that is used to assess pain levels. Moreover, BPI can measure pain related to cancer, chronic disease, psychological disorders, and musculoskeletal conditions, and it has two versions: standard and short form. BPI allows the patient to report the pain intensity, the location of the pain and the pain interference with daily activity [98]. The BPI can aid clinicians, researchers and pharmacies as a clinical monitoring tool for the patient's pain level and its impact on daily functions [99]. Other commonly used self-reported pain measures are numerical pain rating scale (NPRS), visual analogue scale (VAS) and McGill Pain questionnaire (MPQ) [100].

2.5.4 Skeletal burden score

One important recommendation of the international FD/MAS guidelines is the evaluation of FD skeletal extent within the skeleton using a validated semiquantitative tool called skeletal burden score (SBS) [24]. In 2005, Dr Michael Collins and his team developed SBS, which was derived from ^{99m}Tc-MDP bone scintigraphy. The purpose of SBS was to help clinicians assess the severity of FD/MAS in children during diagnosis and understand the disease progression in adulthood [41]. The SBS divides the skeleton into 11 segments (skull, right and left upper extremities, right and left ribs, spine, right and left pelvis, right and left lower extremities the sternum) (Figure 2.4).

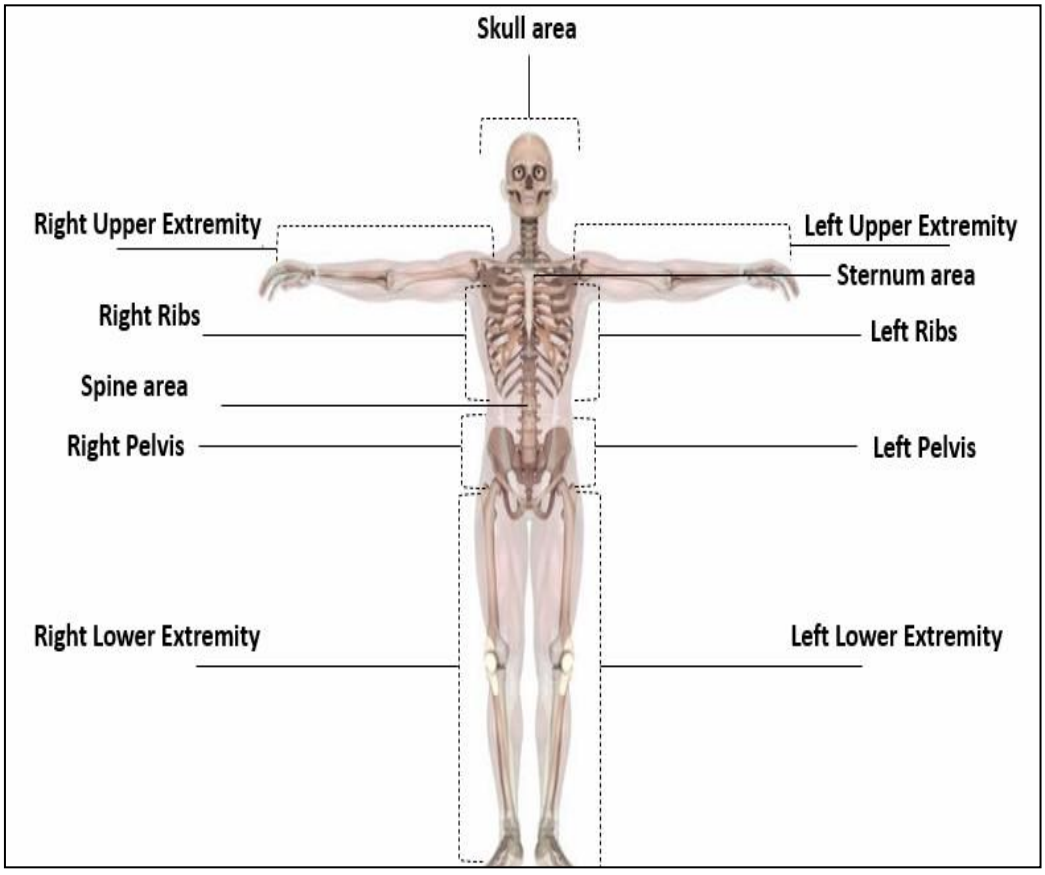


Figure 2.4 Compartments of skeletal burden score
Created with BioRender.com

The percentage FD involvement in each segment is evaluated as follows: 0%, 0-5%= 2.5%, 5-25%=15%, 25-50%= 37.5%, and > 50%= 75%. And then multiplied by the percentage representation of each skeletal segment using the following formula:

Skeletal burden score =

$$(0.184\ x\ skull\ area) + (0.19\ x\ ((right\ upper\ extremity\ area + left\ upper\ extremity))/2)$$
$$+ (0.42\ x\ (right\ lower\ extremity + left\ lower\ extremity\ area)/2)$$
$$+ (0.083\ x\ spine\ area) + (0.044\ x\ (right\ ribs\ area + left\ ribs\ area)/2)$$
$$+ (0.003x\ sternum\ area) + (0.074x\ (right\ pelvis\ area + left\ pelvis\ area)/2)$$

The total SBS ranges from 0 to 75. A high SBS indicates greater disease burden and vice versa. The SBS scores were categorised as follows; mild (0-15), moderate (16-30), severe (31-50) and total FD involvement (51-75) [101]. Previous studies have used the SBS as an assessment tool for skeletal severity, and as a predictor of future functional outcomes in children with FD/MAS [47, 54-56]. SBS is not influenced by age-related changes or the use of bisphosphonate treatment. Furthermore, SBS has been found to correlate with ALP levels, SF-36/CHQ-PF50 [41,55], Cobb angle in cases of scoliosis [58], fracture prevalence [54], walking performance assessed by the 9-minute walk test [102], hip and knee strength, hip rotation and hip fixation [33]. The application of SBS on other nuclear medicine scans beyond bone scintigraphy was an interest of two prospective studies.

Jreige et al. [62] evaluated the FD involvement on ^{99m}Tc-MDP on quantitative SPECT/CT on seven FD patients by calculating the maximum SUV, and the mean SUV. The study aimed to correlate SBS, the maximum and mean SUVs, and the combination of SBS with SUV values with BTM and Cobb angle for scoliosis. No relationship was observed between any of the SUV values with BTM or Cobb angle. Positive correlation observed between SBS with CTX (p=0.01), FGF-23 (p=0.05) and ALP (p=0.06) but not with P1NP (p=0.08), this relationship was stronger with combined with SUV values than SBS alone. On the other hand, Cobb angle was not correlated with any FD involvement measurements. Furthermore, Bruggen et al. [91], evaluated the SBS derived from Na^{18}F-PET/CT scan and correlated with SUV parameters and the measured BTM levels in 20 FD/MAS patients. The study reported that SBS was only correlated with FGF-23, and not with other BTMs. Furthermore, the Na^{18}F volumetric parameters of the fluid tumour volume and the total lesion fluoride along with the SUV values were not correlated with SBS. These studies underscore the potential applicability of SBS across different imaging modalities and suggest future directions for research.

2.6 Summary

The sporadic mosaic nature of FD/MAS, along with its varied clinical manifestations, requires a comprehensive diagnostic evaluation using radiological, clinical, and histological assessments. Measurement of skeletal severity is of parallel importance to diagnostic evaluation. Following the international FD/MAS guidelines for diagnosis, treatment, and management of FD/MAS complications is crucial to effectively address this complex disease.

2.7 References

1. Buckwalter, J.A., et al., *Bone Biology.* JBJS, 1995. **77**(8).
2. Safadi, F.F., et al., *Bone Structure, Development and Bone Biology*, in *Bone Pathology*, J.S. Khurana, Editor. 2009, Humana Press: Totowa, NJ. p. 1-50.
3. Roodman, G.D., *Advances in Bone Biology: The Osteoclast*.* Endocrine Reviews, 1996. **17**(4): p. 308-332.
4. Rowe, P., A. Koller, and S. Sharma, *Physiology, Bone Remodeling*. 2023: StatPearls Publishing, Treasure Island (FL).
5. Schett, G., K.G. Saag, and J.W.J. Bijlsma, *From bone biology to clinical outcome: state of the art and future perspectives.* Annals of the Rheumatic Diseases, 2010. **69**(8): p. 1415.
6. Rodan, G.A., *Introduction to bone biology.* Bone, 1992. **13**: p. S3-S6.
7. Florencio-Silva, R., et al., Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. Biomed Res Int, 2015. **2015**: p. 421746.
8. Clarke, B., *Normal Bone Anatomy and Physiology.* Clinical Journal of the American Society of Nephrology, 2008. **3**(Supplement_3): p. S131-S139.
9. Cowan, P.T., M.V. Launico, and P. Kahai, *Anatomy, Bones*, in *StatPearls*. 2024, StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.: Treasure Island (FL).
10. HADJIDAKIS, D.J. and I.I. ANDROULAKIS, *Bone Remodeling.* Annals of the New York Academy of Sciences, 2006. **1092**(1): p. 385-396.
11. Dumitrescu, C.E. and M.T. Collins, *McCune-Albright syndrome.* Orphanet Journal of Rare Diseases, 2008. **3**(1): p. 12.
12. Boyce, A.M., *Fibrous Dysplasia*, in *Endotext*, K.R. Feingold, et al., Editors. 2000, MDText.com, Inc. Copyright © 2000-2024, MDText.com, Inc.: South Dartmouth (MA).
13. Chapurlat, R.D. and P.J. Meunier, *Fibrous dysplasia of bone.* Best Practice & Research Clinical Rheumatology, 2000. **14**(2): p. 385-398.
14. Chapurlat, R.D. and P. Orcel, *Fibrous dysplasia of bone and McCune-Albright syndrome.* Best Pract Res Clin Rheumatol, 2008. **22**(1): p. 55-69.
15. Kransdorf, M.J., J. R P Moser, and F.W. Gilkey, *Fibrous dysplasia.* RadioGraphics, 1990. **10**(3): p. 519-537.
16. Riddle, N.D. and M.M. Bui, *Fibrous dysplasia.* Arch Pathol Lab Med, 2013. **137**(1): p. 134-8.
17. Williams, D.M.L. and R.S.A. Thomas, *Fibrous dysplasia.* The Journal of Laryngology & Otology, 1975. **89**(4): p. 359-374.
18. *ALBRIGHT'S SYNDROME.* Annals of Internal Medicine, 1952. **37**(3): p. 587-593.
19. LICHTENSTEIN, L., *POLYOSTOTIC FIBROUS DYSPLASIA.* Archives of Surgery, 1938. **36**(5): p. 874-898.
20. Belaval, G.S. and R.W. Schneider, *Fibrous dysplasia of bone.* Cleve Clin Q, 1954. **21**(3): p. 15868.
21. Lee, J.S., et al., *Clinical guidelines for the management of craniofacial fibrous dysplasia.* Orphanet J Rare Dis, 2012. **7 Suppl 1**(Suppl 1): p. S2.
22. Michienzi, S., et al., GNAS transcripts in skeletal progenitors: evidence for random asymmetric allelic expression of Gs alpha. Hum Mol Genet, 2007. **16**(16): p. 1921-30.
23. Weinstein, L.S., G(s)alpha mutations in fibrous dysplasia and McCune-Albright syndrome. J Bone Miner Res, 2006. **21 Suppl 2**: p. P120-4.
24. Robinson, C., M.T. Collins, and A.M. Boyce, *Fibrous Dysplasia/McCune-Albright Syndrome: Clinical and Translational Perspectives.* Curr Osteoporos Rep, 2016. **14**(5): p. 178-86.
25. Feller, L., et al., *The nature of fibrous dysplasia.* Head & Face Medicine, 2009. **5**(1): p. 22.
26. Spencer, T., et al., *The Clinical Spectrum of McCune-Albright Syndrome and Its Management.* Horm Res Paediatr, 2019. **92**(6): p. 347-356.
27. Fourie, J., et al., *Fibrous dysplasia: A tale of two syndromes.* SA J Radiol, 2024. **28**(1): p. 2877.

28. Paul, S.M., et al., Disease severity and functional factors associated with walking performance in polyostotic fibrous dysplasia. Bone (New York, N.Y.), 2014. **60**: p. 41-47.
29. Boyce, A.M., N. Bhattacharyya, and M.T. Collins, *Fibrous dysplasia and fibroblast growth factor23 regulation.* Curr Osteoporos Rep, 2013. **11**(2): p. 65-71.
30. Couturier, A., et al., *[Craniofacial fibrous dysplasia].* Rev Med Interne, 2016. **37**(12): p. 834-839.
31. Hanifi, B., et al., *Craniofacial fibrous dysplasia.* Clin Imaging, 2013. **37**(6): p. 1109-15.
32. Zeng, H.F., et al., Surgical treatment of craniomaxillofacial fibrous dysplasia: functionally or aesthetically? J Craniofac Surg, 2013. **24**(3): p. 758-62.
33. Javaid, M.K., et al., Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis, 2019. **14**(1): p. 139.
34. Collins, M.T., F.R. Singer, and E. Eugster, *McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia.* Orphanet J Rare Dis, 2012. **7 Suppl 1**(Suppl 1): p. S4.
35. Szymczuk, V., et al., *Fibrous Dysplasia / McCune-Albright Syndrome*, in *GeneReviews(®)*, M.P. Adam, et al., Editors. 1993, University of Washington, Seattle
Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered.
36. Collins, M.T., et al., An Instrument to Measure Skeletal Burden and Predict Functional Outcome in Fibrous Dysplasia of Bone. Journal of bone and mineral research, 2005. **20**(2): p. 219-226.
37. Benhamou, J., et al., Prognostic factors from an epidemiologic evaluation of fibrous dysplasia of bone in a modern cohort: the FRANCEDYS study. Journal of Bone and Mineral Research, 2016. **31**(12): p. 2167-2172.
38. rechte Oberschenkelbein, D., *Fall von Ostitis fibrosa mit multiplen Tumoren in der umgebenden Muskulatur.* Verhandlungen der Deutschen Pathologischen Gesellschaft, 1926. **21**: p. 93.
39. Mazabraud, A., Apropos of the association of fibromyxomas of the soft tissues with fibrous dysplasia of the bones. Presse Med, 1967. **75**: p. 2223-2228.
40. Majoor, B.C.J., et al., Prevalence and Clinical Features of Mazabraud Syndrome: A Multicenter European Study. JBJS, 2019. **101**(2).
41. Kitagawa, Y., et al., *Mazabraud syndrome associated with McCune–Albright syndrome.* Journal of Orthopaedic Science, 2011. **16**(1): p. 129-132.
42. Majoor, B.C.J., et al., Determinants of impaired quality of life in patients with fibrous dysplasia. Orphanet J Rare Dis, 2017. **12**(1): p. 80.
43. Spencer, T.L., et al., *Neuropathic-like Pain in Fibrous Dysplasia/McCune-Albright Syndrome.* J Clin Endocrinol Metab, 2022. **107**(6): p. e2258-e2266.
44. Majoor, B.C.J., et al., Pain in fibrous dysplasia: relationship with anatomical and clinical features. Acta Orthop, 2019. **90**(4): p. 401-405.
45. Kelly, M.H., B. Brillante, and M.T. Collins, Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions. Osteoporos Int, 2008. **19**(1): p. 57-63.
46. Demontiero, O., C. Vidal, and G. Duque, *Aging and bone loss: new insights for the clinician.* Ther Adv Musculoskelet Dis, 2012. **4**(2): p. 61-76.
47. Berkley, K.J., *Sex differences in pain.* Behavioral and Brain Sciences, 1997. **20**(3): p. 371-380.
48. Hartley, I., et al., Fibrous Dysplasia of Bone and McCune-Albright Syndrome: A Bench to Bedside Review. Calcif Tissue Int, 2019. **104**(5): p. 517-529.
49. Leet, A.I., et al., Fracture incidence in polyostotic fibrous dysplasia and the McCune-Albright syndrome. J Bone Miner Res, 2004. **19**(4): p. 571-7.
50. Kelly, M.H., et al., Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone. Bone, 2005. **37**(3): p. 388-94.
51. Hart, E.S., et al., Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. J Bone Miner Res, 2007. **22**(9): p. 1468-74.
52. Mancini, F., et al., *Scoliosis and spine involvement in fibrous dysplasia of bone.* Eur Spine J, 2009. **18**(2): p. 196-202.

53. Berglund, J.A., et al., Scoliosis in Fibrous Dysplasia/McCune-Albright Syndrome: Factors Associated With Curve Progression and Effects of Bisphosphonates. Journal of Bone and Mineral Research, 2018. **33**(9): p. 1641-1648.
54. Ruggieri, P., et al., *Malignancies in fibrous dysplasia.* Cancer, 1994. **73**(5): p. 1411-1424.
55. Qu, N., et al., Malignant Transformation in Monostotic Fibrous Dysplasia: Clinical Features, Imaging Features, Outcomes in 10 Patients, and Review. Medicine, 2015. **94**(3).
56. Javaid, M.K., et al., Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis, 2019. **14**(1): p. 139.
57. Jreige, M., et al., A novel approach for fibrous dysplasia assessment using combined planar and quantitative SPECT/CT analysis of Tc-99m-diphosphonate bone scan in correlation with biological bone turnover markers of disease activity. Frontiers in Medicine, 2022. **9**.
58. DiCaprio, M.R. and W.F. Enneking, *Fibrous dysplasia. Pathophysiology, evaluation, and treatment.* J Bone Joint Surg Am, 2005. **87**(8): p. 1848-64.
59. Burke, A.B., M.T. Collins, and A.M. Boyce, *Fibrous dysplasia of bone: craniofacial and dental implications.* Oral Dis, 2017. **23**(6): p. 697-708.
60. Adetayo, O.A., et al., Fibrous dysplasia: an overview of disease process, indications for surgical management, and a case report. Eplasty, 2015. **15**: p. e6.
61. Shi, R.-R., et al., GNAS mutational analysis in differentiating fibrous dysplasia and ossifying fibroma of the jaw. Modern Pathology, 2013. **26**(8): p. 1023-1031.
62. Sundaram, M., *Imaging of Paget's Disease and Fibrous Dysplasia of Bone.* Journal of Bone and Mineral Research, 2006. **21**(S2): p. P28-P30.
63. Kushchayeva, Y.S., et al., *Fibrous dysplasia for radiologists: beyond ground glass bone matrix.* Insights Imaging, 2018. **9**(6): p. 1035-1056.
64. Atalar, M.H., et al., CT and MR Imaging in a Large Series of Patients with Craniofacial Fibrous Dysplasia. Pol J Radiol, 2015. **80**: p. 232-40.
65. Thomsen, M.D. and L. Rejnmark, Clinical and radiological observations in a case series of 26 patients with fibrous dysplasia. Calcif Tissue Int, 2014. **94**(4): p. 384-95.
66. Daffner, R.H., et al., *Computed tomography of fibrous dysplasia.* AJR Am J Roentgenol, 1982. **139**(5): p. 943-8.
67. MacDonald-Jankowski, D.S., et al., *Computed tomography of fibrous dysplasia.* Dentomaxillofac Radiol, 2004. **33**(2): p. 114-8.
68. Bulakbaşi, N., et al., CT and MRI in the evaluation of craniospinal involvement with polyostotic fibrous dysplasia in McCune-Albright syndrome. Diagnostic and Interventional Radiology, 2008. **14**(4): p. 177-181.
69. Park, S.K., et al., *CT and MRI of fibrous dysplasia of the spine.* British Journal of Radiology, 2012. **85**(1015): p. 996-1001.
70. Shah, Z., et al., *Magnetic resonance imaging appearances of fibrous dysplasia.* The British journal of radiology, 2005. **78**(936): p. 1104-1115.
71. Pekcevik, Y., M. Kahya, and A. Kaya, Diffusion-weighted magnetic resonance imaging in the diagnosis of bone tumors: Preliminary results. Journal of Clinical Imaging Science, 2013. **3**(1).
72. Zhibin, Y., et al., *The Role of Radionuclide Bone Scintigraphy in Fibrous Dysplasia of Bone.* Clinical Nuclear Medicine, 2004. **29**(3): p. 177-180.
73. Papadakis, G.Z., et al., *18F-NaF PET/CT imaging in fibrous dysplasia of bone.* Journal of Bone and Mineral Research, 2019. **34**(9): p. 1619-1631.
74. Zhang, L., et al., *99Tcm-MDP SPECT/CT imaging in diagnosis of fibrous dysplasia.* Chinese Journal of Medical Imaging Technology, 2016. **32**(7): p. 1102-1105.
75. Aras, M., et al., False positive FDG PET/CT resulting from fibrous dysplasia of the bone in the work-up of a patient with bladder cancer: case report and review of the literature. Iranian Journal of Radiology, 2013. **10**(1): p. 41.

76. Pan, B. and S.C. Wang, *18F-FDG PET findings of a case of polyostotic fibrous dysplasia.* Interdisciplinary Neurosurgery: Advanced Techniques and Case Management, 2021. **23**.
77. Fisher, D.R. and F.H. Fahey, Appropriate Use of Effective Dose in Radiation Protection and Risk Assessment. Health Phys, 2017. **113**(2): p. 102-109.
78. Mettler, F.A., et al., Effective Doses in Radiology and Diagnostic Nuclear Medicine: A Catalog. Radiology, 2008. **248**(1): p. 254-263.
79. van der Bruggen, W., et al., *Quantifying skeletal burden in fibrous dysplasia using sodium fluoride PET/CT.* Eur J Nucl Med Mol Imaging, 2020. **47**(6): p. 1527-1537.
80. Chapurlat, R.D., et al., *Pathophysiology and medical treatment of pain in fibrous dysplasia of bone.* Orphanet J Rare Dis, 2012. **7 Suppl 1**(Suppl 1): p. S3.
81. Stanton, R.P., et al., *The surgical management of fibrous dysplasia of bone.* Orphanet J Rare Dis, 2012. **7 Suppl 1**(Suppl 1): p. S1.
82. Fukumoto, S., FGF23-related hypophosphatemic rickets/osteomalacia: diagnosis and new treatment. Journal of Molecular Endocrinology, 2021. **66**(2): p. R57-R65.
83. Roszko Kelly, L., T. Collins Michael, and M. Boyce Alison, *Mosaic Effects of Growth Hormone on Fibrous Dysplasia of Bone.* New England Journal of Medicine, 2018. **379**(20): p. 1964-1965.
84. Chakraborty, D., et al., *Radioiodine treatment in McCune-Albright syndrome with hyperthyroidism.* Indian J Endocrinol Metab, 2012. **16**(4): p. 654-6.
85. Bullinger, M. and J. Quitmann, *Quality of life as patient-reported outcomes: principles of assessment.* Dialogues Clin Neurosci, 2014. **16**(2): p. 137-45.
86. Bonafé, F.S.S., et al., *Brief Pain Inventory: A proposal to extend its clinical application.* European Journal of Pain, 2019. **23**(3): p. 565-576.
87. Cleeland, C. and K. Ryan, *Pain assessment: global use of the Brief Pain Inventory.* Annals of the Academy of Medicine, Singapore, 1994. **23**(2): p. 129-138.
88. Szymczuk, V., et al., Skeletal Disease Acquisition in Fibrous Dysplasia: Natural History and Indicators of Lesion Progression in Children. Journal of Bone and Mineral Research, 2022. **37**(8): p. 1473-1478.
89. Paul, S.M., et al., Disease severity and functional factors associated with walking performance in polyostotic fibrous dysplasia. Bone, 2014. **60**: p. 41-7.

Thesis objectives

- To systematically review the literature on the relationship between SBS and physical outcomes in patients with FD/MAS.
- To systematically review the diagnostic accuracy of cross-sectional imaging modalities in the assessment of FD.
- To evaluate clinicians' knowledge and use of the SBS when diagnosing FD amongst clinicians (radiologists, endocrinologists, orthopaedics and pedestrians)
- To investigate the relationship between SBS and the health-related (QoL) and pain in a cohort of Saudi FD/MAS patients.
- To assess the physical, emotional, and social impact of FD/MAS on Saudi patients using QoL questionnaires and bone pain assessment tool with six-months follow-up.
- To determine the inter- and intra- reader agreement in applying SBS to bone scintigraphy. the reliability and the inter- and intra-reader agreement of the use of SBS among five readers.
- To evaluate the applicability and reliability of SBS on WB-MRI in comparison with bone scintigraphy.

Chapter 3:

What Is the Correlation Between Skeletal Burden Score and Functional Outcome in Patients with Fibrous Dysplasia? A Systematic Review and Meta-Analysis

3.1 Abstract

Purpose:
To determine the relationship between skeletal burden score (SBS) and physical outcomes measured by health-related quality of life (HRQoL) in patients with fibrous dysplasia/McCune-Albright syndrome (FD/MAS).

Methods:
The following databases were systematically reviewed: PubMed, SCOPUS, Web of Science, Medline via Ovid, Cochrane Library, and Google Scholar for studies published between February 2005 and March 2024. All studies measuring the QoL of patients diagnosed with FD/MAS, reporting HRQoL scores, and correlating HRQoL with SBS were included. The quality of the eligible studies was assessed using the National Heart, Lung, and Blood Institute (NHLBI) tool. Contingency tables were constructed to summarise the HRQoL scores, SBS and the main findings. The relationship between SBS and Short Form-36 (SF-36) QoL measures was pooled using random-effects models.

Results:
Out of the 25 studies initially identified, seven were deemed suitable for inclusion. Most of the included studies utilised the SF-36 for adults, and the CHQ-PF50 for children. The HRQoL scores of FD/MAS were significantly lower than those of the reference standard population in particular domains of physical health across the included studies. Correlations were reported between SBS with SF-36/CHQ-PF50, PODCI, and IPQ-R but not with UCL questionnaire. Four studies were included in the meta-analysis, demonstrated a mean difference of - 0.42 (95% confidence interval (CI) = - 0.51 - 0.31, I^2 = 14%).

Conclusion:
This systematic review highlights the significant impact of FD/MAS on patients' physical health and underscores the strong association between high SBS and poorer physical outcomes. The findings support the clinical utility of SBS in assessing disease severity and predicting physical function. Future research should focus on validating disease-specific HRQoL tools and conducting longitudinal studies to further explore the predictive value of SBS for long-term patient outcomes.

3.2 Introduction

Fibrous dysplasia (FD) is a rare, non-inherited metabolic bone disease caused by the mutation in the guanine nucleotide-binding alpha-stimulating (GNAS) gene. This mutation leads to the formation of abnormal expansile fibro-osseous lesions in normal bone, which can be single FD lesion (monostotic FD) or more multiple FD lesions (polyostotic FD) [1, 2]. In addition, FD can be associated with extra- skeletal manifestations such as café-au-lait spots and endocrinopathies; this condition is called McCune-Albright syndrome (MAS) [2]. Patients with FD/MAS can experience bone pain, pathological fractures, bone deformities, progressive scoliosis, and functional impairment [2]. The clinical spectrum of FD/MAS is wide, ranging from asymptomatic monostotic FD lesion found accidentally during imaging for another abnormality to polyostotic FD lesions that affect the individual's ability to move independently. Moreover, extensive FD involvement in the lower extremities may lead to functional impairment due to the high risk of fractures in weight-bearing bones and the requirement for ambulatory assistive devices, such as crutches, canes, and wheelchairs [3, 4].

The skeletal burden score (SBS) is the only validated tool for assessing skeletal severity in FD/MAS, quantifying the extent of FD involvement across different skeletal compartments. Unlike other measures, the SBS is unaffected by age-related changes or the use of bisphosphonate treatments [5]. The scoring system assigns a specific weight to each skeletal region based on its functional importance and the degree of FD involvement within that region. Importantly, the SBS is not determined by the number or size of individual lesions but by the overall percentage of skeletal involvement in each

compartment. SBS has been widely used in studies to assess disease severity and has demonstrated strong correlations with bone turnover markers (BTM) [6-8], disease progression [9, 10], treatment outcomes [11], and functional performance [12]. Its reliable and accessible nature makes it a valuable tool for clinical assessment and research.

The evaluation of an individual's quality of life (QoL) is a crucial aspect in comprehending the impact of rare diseases on the physical and mental health. A limited number of studies have investigated the health-Related Quality of Life (HRQoL) of FD/MAS; To date, no systematic review has comprehensively examined the relationship between SBS and HRQoL in FD patients, highlighting a critical gap in the literature. Therefore, this review aimed to summarise the QoL of FD/MAS. Second, we conducted a meta-analysis that investigated the association between SBS and the physical component of quality of life in patients with FD/MAS.

3.3 Materials and Methods

This systematic review was registered in the Prospective Register of Systematic Reviews (PROSPERO database; register number # CRD42021242019) on 22 March 2021. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. The research question was, “What is the relationship between the SBS, and physical functions measured by HRQoL assessment in patients with FD/MAS? “.

3.3.1 Search strategy

A computer search was performed using the following databases: MEDLINE via Ovid, PubMed, Web of Science, SCOPUS, Cochrane Library, and Google Scholar. Furthermore, the reference lists of the included papers were screened to identify any additional relevant studies. The search terms were framed using the Population, Intervention, Comparator, and Outcome (PICO) format. Patients/population (P): Children and adults diagnosed with FD/MAS. Intervention (I): SBS was derived from bone scintigraphy scans. Comparator (C): No comparator in this review. Outcome (O): Physical function was assessed using validated HRQoL measures, and ambulatory status (if available) which is usually extracted from the patient's medical notes. We used Boolean operators with the following search terms: (Fibrous dysplasia OR monostotic fibrous dysplasia OR polyostotic fibrous dysplasia OR McCune-Albright syndrome OR "FD" OR "FD/MAS"), AND (Skeletal burden score OR 'SBS' OR 'SDBS'); AND (Quality of life OR health-related quality of life OR physical function OR function outcomes).

To be eligible for inclusion, studies were required to meet the following criteria: a) original studies, including adults and children diagnosed with FD/MAS; b) studies that used SBS as a clinical tool for measuring skeletal severity; c) studies that used validated HRQoL at least at a single time point or the report of ambulatory status; d) studies written in English and published between 2005 and March 2024; and e) studies published in a peer-reviewed journal. This review excluded clinical trials, review articles, case studies, conference proceedings, abstracts, and full-text papers that could not be retrieved. The initial search was conducted by a single reviewer (A.A.) who independently screened the

titles and abstracts and retrieved full-text papers from the eligible papers. A second reviewer (A.O.) reviewed the eligible papers based on the inclusion and exclusion criteria. Any discrepancies or uncertainties were resolved through discussion with a third reviewer (A.R.). The search references were exported to EndNote bibliographic manager software version 20.0, where duplicate references were removed electronically.

3.3.2 Data extraction

A single reviewer (A.A.) extracted the data of the included studies, including the primary author, year of publication, country, study design, sample size, age group, FD subtype, Skeletal severity measures, HRQoL measures, and main findings. Another reviewer (A.O.) checked the extracted data for their accuracy.

3.3.3 Quality assessment

We used the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-sectional studies [14] to assess the quality of the included studies. The NHLBI tool consists of 14 items and an overall quality rating for each study (poor, fair, or good), indicating each study's risk of bias owing to methodological flaws. All three reviewers independently assessed the quality of the included studies and were blinded to each other's decision. Discrepancies between the reviewers were resolved by consensus.

3.3.4 Data synthesis

The meta-analysis summarised the effects, considering the relationship between SBS and the physical functioning domain of the QoL measures. To conduct a meta-analysis using random effects, we first transformed the correlation coefficients from each study into Fisher's z-scores (Z-COR) to stabilise the variance and normalise the distribution [15]. This transformation is critical because the sampling distribution of the correlation coefficients can be skewed, particularly when the correlations are near the scale's extremes. By converting these coefficients into Z-COR, we facilitated more accurate pooling of data across studies. Once all individual study correlations were transformed to Z-COR, we performed a random-effects meta-analysis to account for both within-study and between-study variability and estimate the pooled correlation.

This model is appropriate, given the potential in study populations, methodologies, and other factors that could introduce heterogeneity. Heterogeneity (I^2), which is the variation across the included studies, ranges from 0% to 100%; the greater the percentage, the greater the magnitude of heterogeneity [16]. Heterogeneity with < 25% was considered low, 50% was medium, and >75% was considered high [17]. visual inspection of heterogeneity is presented in the funnel plots. The estimated pooled correlation was presented as a 95% confidence interval (CI) for each included study. Publication bias analysis was the second component of this meta-analysis. Publication bias occurs when studies with no statistical significance may not be published, simply because the journals or research favour positive, significant studies.

Rosenthal first introduced fail-safe N calculations in 1979 [18], which were used to assess the robustness of meta-analysis results by estimating the number of additional studies with null results (effect size of zero) that would be required to bring the overall result to a non-significant level [19]. Fail-safe N denotes the number of additional studies with negative findings to increase the significance of the p-value (0.05), which frequently overestimates the statistical significance. Hence, funnel plots are the best approach for visually assessing publication bias [20]. The meta-analysis was performed using R software version 4.0.3.

3.4 Results

Figure 3.1 outlines the search strategy in accordance with PRISMA 2020. The comprehensive search was conducted across six databases. A total of 406 papers were initially identified. After removing duplicates using EndNote, 36 unique studies remained and were subjected to screening of the titles and abstracts based on the inclusion and exclusion criteria. Of these, 16 full-text articles were retrieved for detailed review. Each paper was critically evaluated to determine whether it met the necessary methodological and clinical criteria. During this process, nine studies were excluded for specific reasons, including the absence of SBS as an assessment tool, lack of validated QoL measures, being a review article rather than original research, or focusing solely on treatment outcomes rather than functional outcomes.

Ultimately, seven studies met the eligibility criteria [5, 21-26], demonstrating relevance to the research objectives. Among these, four studies provided sufficient data for inclusion in the meta-analysis [5, 22, 25, 26], ensuring a robust quantitative synthesis of findings related to skeletal severity and QoL outcomes.

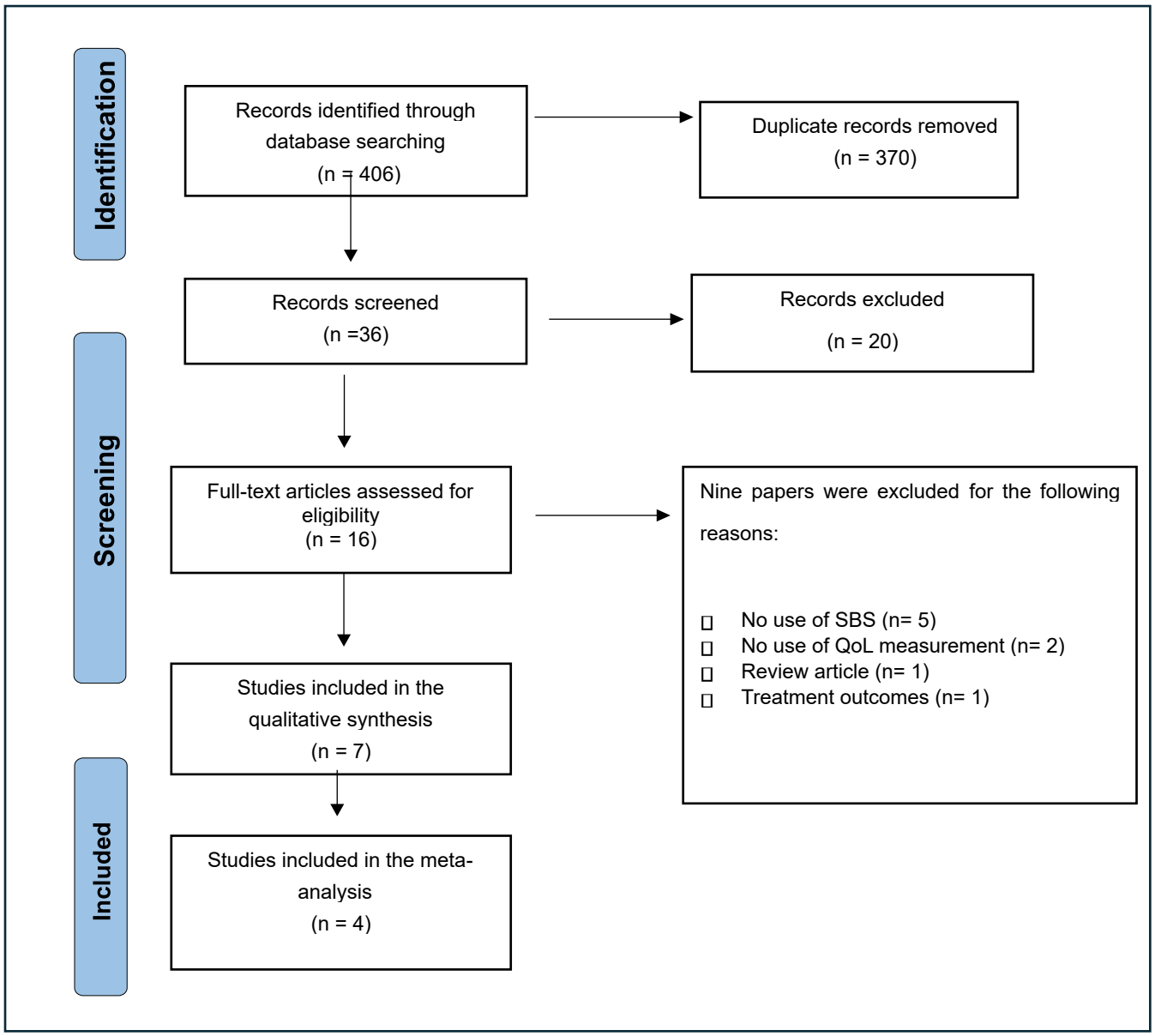


Figure 3.1 The flow chart of the studies selection according to the PRISMA statement

3.4.1 General characteristics of the included studies

The general characteristics of the included studies are presented in Table 3.1. Four studies originated in the Netherlands [22-24, 26], and the remaining three studies were conducted in the United States of America (USA) [5, 21, 25]. The studies conducted in the USA were based on data from the National Institute of Health's (NIH) longstanding cohort of children and adult diagnosed with FD/MAS. In contrast, the studies from the Netherlands were based on another longstanding FD/MAS adult cohort at Leiden University Medical Centre (LUMC). Although all the included studies were drawn from two large patient cohorts, four studies presented original findings [5, 22, 25, 26], while the remaining three studies reused the same patient cohort and partial of the results to investigate different aspects such as different outcome measures or questionnaires [21, 23, 24].

All the included studies enrolled patients with confirmed diagnosis of FD, based on clinical history, radiological findings, and histopathological confirmations. Within the included studies, we identified four HRQoL instruments used; Short-form 36 (SF-36) [5, 22, 25, 26]; paediatric outcomes data collection instrument (PODCI) [21]; illness perception of questionnaire-revised (IPQ-R) [23]; Utrecht coping list (UCL) [24].

Table 3.1 Characteristics and main findings of the included studies

Author (year)	Patient Cohort	Sample Size (female n)	Age group	Type of FD	FD severity tools	Outcome measure	Main Findings
Collins et al. (2005) [5]	NIH	79 (53)	Children and adults	All FD subgroup	SBS, BTM	SF-36, CHQ-PF50, ambulatory status	• SBS correlated with ALP (r= 0.67) • SBS correlated with physical functioning domain of SF-36 (r= -0.43, p=0.001). • The SBS of individuals who used ambulatory assistive devices were higher than the ones who ambulate independently. • High SBS (>30) in childhood was linked with functional impairment in adulthood.
Kelly et al. (2005) [25]	NIH	78 (48)	Children and adults	All FD subgroup	SBS	SF-36, CHQ-PF50	• QoL physical component scores were lower in the FD population compared with the USA population. • In adults, precocious puberty correlated with low PF (p=0.031) and high SBS (p=0.035). • In children, hyperthyroidism correlates with low PF (p=0.0018) and high SBS (p=0.0381). • No differences were noted in the scores of MH and RE domains between FD patients and the US population.
Leet et al. (2006) [21]	NIH	20 (8)	Children and adolescent	MAS and PFD	SBS	PODCI	• FD population scores were lower in sports and happiness than in the US population. • SBS of lower extremities correlated negatively with transfer (r=0.76, p=0.03) and sports domain (r=0.77, p=0.02). • Total SBS did not correlate with any of the PODCI components.
Majoor et al. (2017) [22]	LUMC	97 (63)	Adults	All FD subgroups	SBS, FGF-23, BTM	SF-36	• QoL physical component scores were lower in the FD population compared with the Dutch population. • MAS QoL had the lowest, followed by PFD and MFD.

							Negative correlation between FGF-23 and PF QoL (r=-0.49, p<0.001).
Majoor et al. 2018[23]	LUMC	97 (63)	Adults	All FD subgroups	SBS, FGF-23	IPQ-R	• High FGF-23 correlated with high identity and consequences domains in IPQ-R. • High SBS correlated with higher consequences IPQ-R. • IPQ-R scores correlated with SF-36 QoL.
Rotman et al. 2018 [24]	LUMC	92 (61)	Adults	All FD subgroups	SBS, BTM	UCL	• There is no correlation between SBS or ALP and UCL. • There is no significant difference in coping strategies between FD subgroups. • FD patients reported lower scores in expressing emotions and seeking social support than the reference population.
Meier et al. 2022 [26]	LUMC	92(61)	Adults	All FD subgroups	SBS	SF-36, BPI	• The overall SF-36 scores of FD/MAS patients were lower than the general population. • Improvement of SF-36 after 12 months follow-up. • The multidisciplinary pathway improved the QoL and the severity of the pain.

Abbreviations; ALP, alkaline phosphatase; BTM, bone turnover marker; CHQ-PF50, child health questionnaire; FD, fibrous dysplasia; FGF-23, fibroblast growth factor-23; IPQ-R, illness perception of questionnaire-revised; LUMC, Leiden University Medical Centre; MAS, McCune-Albright syndrome; MFD, monostotic fibrous dysplasia; NIH, the National Institute of Health; PFD, polyostotic fibrous dysplasia; PODCI, paediatric outcomes data collection instrument; SBS, skeletal burden score; SF-36, short-form health quality of life-36; UCL, Utrecht coping list questionnaire.

3.4.2 The impact of fibrous dysplasia on the quality of life

Four of the included studies used SF-36 [5, 22, 25, 26]. The SF-36 is a widely used generic instrument for measuring the QoL of patients with various conditions, including healthy individuals, in research settings. [27, 28]. SF-36 contains 36 questions divided into eight domains: physical function, role-physical, bodily pain, general health, vitality, mental health, role-emotional, and social functions. The SF-36 scores of the individuals with FD/MAS were found to be lower than the reference standards from the Netherlands and the USA. Moreover, Kelly et al. [25] compared the SF-36 scores of the NIH patient cohort to the American reference standard, finding that the physical function (40 vs. 50), physical role (43 vs. 50), bodily pain (43 vs. 50), and general health (44 vs. 50) domains had the lowest scores. Vitality, social functioning, mental health, and emotional-role domains were like the reference standard. This finding is in line with the results of another study in the Netherlands by Majoor et al. [22] compared the QoL of the LUMC cohort with that of the Dutch reference standard. The SF-36 domains that had lower scores than the reference standard included physical health (75 vs. 83), physical role (66 vs. 76), bodily pain (68 vs. 75), general health (59 vs. 71), vitality (61 vs. 69), and social functioning (77 vs. 84). In addition, MAS patients scored lower on the SF-36 in the physical function and physical role domains compared to polyostotic and monostotic FD [22], showing that the more severe the FD disease, the worse the physical functioning.

In children with FD, two studies used the 50-item child-health questionnaire (CHQPF50) [5, 22]. The CHQ-PF50 is a generic QoL scale designed to measure children's quality of life between the ages of 5 and 18. The CHQ-PF50 includes two proxies: parents and children. For the child proxy, the CHQ-PF50 was designed with the same domains as the SF-36. The parent CHQ-PF50 proxy is divided into ten domains: physical function, role-physical, general health, bodily pain, role-emotional, parental tome, parental emotional, self-esteem, mental health, and behaviour domains. Kelly et al. [25] used CHQ-PF50 to measure QoL in the paediatric FD cohort. The physical function domain of the patient cohort compared with the reference standard was (72 vs. 96), general health (55 vs. 75), and bodily pain (64 vs. 82). Moreover, the emotional domain of the parent proxy was lower than that of the reference population. On the other hand, role physical, role-emotional, parental time, self-esteem, behaviour, and mental health domains were found to be different from those of the American population. Increased of a BTM called procollagen type 1 N-propeptide (P1NP) were correlated with low general health domain scores ($p = 0.01$) and low emotional role domains ($p = 0.001$).

Meier et al. [26] investigated the QoL and pain of 92 long-term LUMC and Radboud University Medical Centre (RUMC) patients diagnosed with FD/MAS at the start of the study, and again after 12 months. The study was conducted between 2018 and 2021. This study aimed to assess the impact of implementing the recent multidisciplinary care pathway presented by the international FD/MAS guidelines on the QoL of the patient cohort [29]. This multidisciplinary pathway comprises clinicians from diverse specialties, who possess extensive expertise in FD/MAS, to collaborate and coordinate the management of FD-

related complications as a unified team. The pathway was applied to the Netherlands' tertiary centres, LUMC, and RUMC. The study consisted of measuring QoL using the SF-36 or EuroQoL 5D-3L (EQ-5D), and assessing pain using the Brief pain inventory (BPI) and IPQ-R. The SF-36 domain scores of the patient cohort were lower than those of the Dutch population. The physical SF-36 domain was reported to have the lowest score, whereas social functioning had the highest score (Table 3.3). The SBS was correlated with physical functioning domains (Spearman's rho = -0.281, p = 0.007). No changes were noted in the IPQ-R between the study's baseline and follow-up phases, indicating that the multidisciplinary care approach did not affect patients' perceptions of FD/MAS. It has also been demonstrated that incorporating FD/MAS guidelines into a care pathway improves overall QoL, especially in the physical, role, and social functioning domains. Additionally, there was a decrease in the reported levels of severe pain and pain interference.

The study by Leet et al. [21] also examined the reported PODCI scores of children and adolescents with FD/MAS. PODCI is a validated questionnaire designed to evaluate the effects of an illness on a child's physical abilities. The PODCI is divided into six scales: happiness, transfer and modality, sports and physical functions, pain, and global and upper extremities to perform daily functions. Both the child and the parent completed the PODCI. There are two paediatric versions of the PODCI: the child version, designed for children ten years of age and younger, and the adolescent version [22]. Leet et al. [21] also looked at the PODCI in relation to other clinical data such as the femoral neck shaft angle (which is often smaller in FD; this is called the "shepherd's crook" on X-rays), Cobb angle, scoliosis, number of fractures, degree of bone deformity, and the presence of endocrinopathy. The

sports PODCI scale, followed by the happiness, were reported to be the lowest of the patient cohort. Similarly, a decreased femoral neck-shaft angle was correlated with the "sports" scale ($r = 0.46$, $p = 0.03$), demonstrating that FD affected the ability to perform daily activities in children and adolescents with FD/MAS. No correlation was found between the PODCI scores and fractures, scoliosis, endocrinopathy, or deformity.

The study of Majoor et al. [23] used the IPQ-R to evaluate individuals' health perceptions. In addition, the study compared the FD/MAS results with those of people with acute pain, chronic pain, fibromyalgia, and acromegaly. IPQ-R consists of three domains: illness identity and the associated symptoms, beliefs about the disease timeline and characteristics, and the consequences of the disease on physical and mental functions [23]. In all IPQ-R domains, patients with MAS had worse illness perceptions than those with polyostotic and monostotic FD. In addition, the research showed a connection between FD symptoms and both the SF36 physical functioning domain ($r = -0.52$, $p<0.001$) and bodily pain ($r = -0.58$, $p<0.001$). This indicates that FD complications are associated with poor functional outcomes. Rotman et al. [24] used the UCL to assess the coping strategies used amongst adults with FD and compared the results with two reference groups: randomised Dutch women and nurses, and another group of patients with chronic pain. The study identified seven coping strategies: passive reaction patterns, active confronting, palliative reactions, seeking social support, avoidance, expressing emotions, and reassuring thoughts [25]. Subsequently, this study found that FD patients expressed less emotions, such as anger, fear, and worry, than Dutch women and nurses. The study also found that patients with FD seek distraction, social support, and active coping compared with patients

with chronic pain. Furthermore, compared with the SF-36, active coping and emotional expression were correlated with worse mental health domains. Passive coping was found to be associated with physical function, and bodily pain SF36 domains ($r = -0.36$, $p<0.001$) and ($r = -0.32$, $p<0.01$, respectively) [25].

Table 3.2 The reported SF-36 scores in the included studies

Author, age group / SF-36/CHQ-PF50 domain	Kelly et al, [25] Adults	Kelly et al., [25] Children	Majoor et al., [22], Adults	Meier et al, [26] Adults
Physical functioning	40 (50)	72 (96)	75 (83)	70.2 (83)
Role physical	43 (50)	-	66 (76)	48.4 (76.4)
Vitality	50 (50)	-	61 (69)	51.3 (68.6)
Mental health	50 (50)	-	-	54.7 (76.8)
Role emotional	50 (50)	54 (88)	-	55 (77)
Social functioning	50 (50)	-	77 (84)	71.3 (84)
Bodily pain	43 (50)	64 (82)	68 (75)	61.3 (74.9)
General Health	44 (50)	55 (73)	59 (71)	56.1 (70.7)

The mean score for each SF-36 domain, and in parentheses the mean SF-36 scores of the reference standard.

3.4.3 The relationship between skeletal burden score and clinical variables

The assessment of ambulatory status was included in only one of the included studies. Collins et al. [5] discovered that the SBS of individuals who ambulated without assistance was lower than those who required ambulatory assistive aids. In addition, the mean SBS of patients who ambulated without assistance (n = 53) was 16.3, whereas in patients with crutches (n = 17), the SBS was 45.2, and in patients with wheelchairs (n = 9), the SBS was 64.7.

Collins et al. [5] also emphasized that children with an SBS score greater than 30, which indicates a high SBS score, are likely to require ambulatory assistance aids such as crutches, canes, and wheelchairs. Collins et al. [5] measured the relationship between SBS and different markers of bone metabolism. In addition, SBS showed a strong positive relationship with ALP (0.67), osteocalcin (0.54), pryridinoline (0.66), and N-telopeptide (0.62). This relationship was not observed for SBS, bone-specific ALP, and deoxypyridinoline. Majoor et al. [22] performed a regression analysis between SBS and other clinical variables to identify the predictors of impaired physical functions in the patient cohort. A high SBS was associated with high fibroblast growth factor- 23 (FGF-23) levels ($p = 0.01$) and high P1NP levels ($p = 0.001$).

3.4.4 Outcome measures

Physical function SF-36 domain was correlated with SF-36;(-0.43, p = 0.005) in adults, and (-0.72, p = 0.005) in children [5, 22]. Furthermore, in adults with polyostotic FD and diagnosed with precocious puberty were associated with high SBS (p = 0.035), and lower physical function SF-36 domain (p = 0.031). In children, hyperthyroidism was significantly associated with higher SBS (p = 0.0381), and lower physical function CHQPF50 (p = 0.0018) [25]. A similar relationship was observed between SBS of the lower extremities and some of the PODCI subscales: transfer (r = 0.76, p = 0.03) and sports (r = 0.77, p = 0.02) [21]. On the other hand, no correlation was found between PODCI and the cumulative SBS [21]. A similar relationship was found between the IPQ-R questionnaire and the SBS. The consequence subscale was negatively related to the SBS (-0.35, p=0.003), FGF-23 (-0.37, p=0.007), and physical function SF-36 domain (0.58, p<0.001) [24]. No relationship was measured between UCL domains and SBS, ALP levels, or age changes. [24]. After obtaining the pooled Z-COR, we applied back transformation to convert the summary Z-COR back into a correlation coefficient (COR). This back transformation allows for the interpretation of the results in the original correlation metric, which is more intuitive and meaningful for practical purposes. Four studies were included in the meta-analysis of SBS with physical functioning SF-36 domains [5, 22, 25, 26]. The individual study correlation coefficients range from - 0.51 to - 0.28, with varying confidence intervals indicating the precision of each estimate. The pooled random effects model yielded a summary correlation coefficient of -0.42 with a 95% CI of -0.51 to -0.31, suggesting an overall moderate negative correlation.

Figure 3.2 demonstrated the overall pooled mean scores of the four included studies, with a total sample size of 347 patients with FD. The heterogeneity statistics indicated a low level of between-study variability (I^2 = 14%, τ^2 = 0.0028, p = 0.32), implying that the observed variation in correlation coefficients across studies was not substantial. Figure 3.3 presented the publication bias funnel plot. The meta-analysis results are robust, as indicated by the high fail-safe N of 132 (p<0.001), indicating that publication bias is unlikely to have a significant impact on the overall conclusions, and the funnel plot does not provide evidence of significant publication bias. The studies were symmetrically distributed around pooled effect sizes.

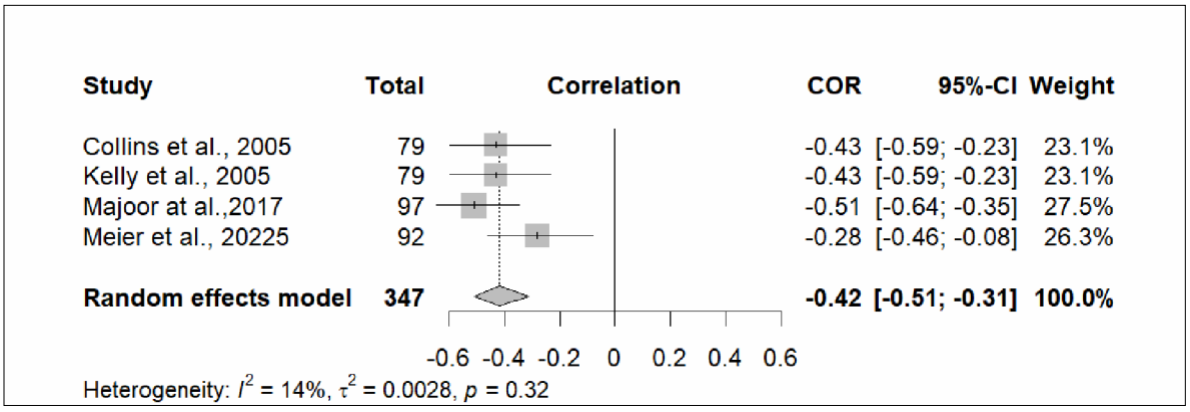


Figure 3.2 Forest plot of the correlation between SBS and the physical domain of the SF-36
Abbreviation; COR, correlation coefficients; CI, confidence interval

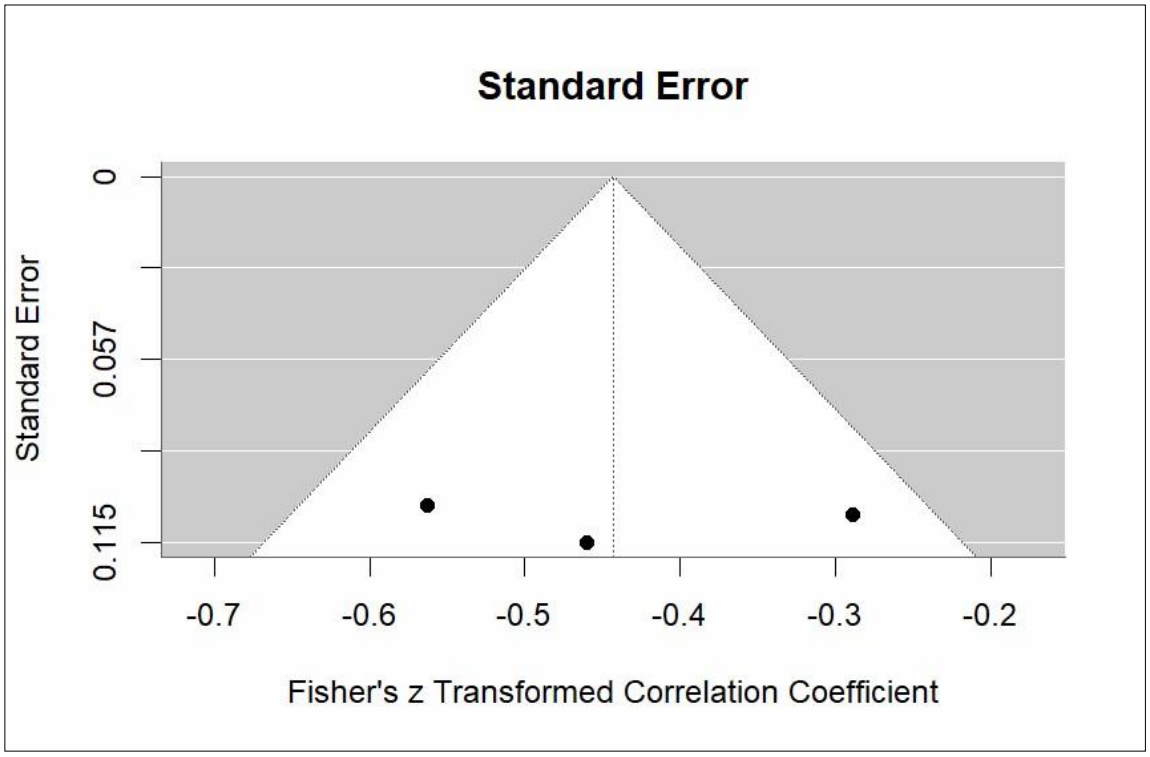


Figure 3.3 Funnel plot for publication bias using Fisher's Z-transformed correlation

3.4.5 Quality assessment

Following the assessment by the three reviewers, five of the included studies [5, 21-23, 25, 26] had "good" methodological quality, indicating a low risk of bias. One study [25] was found to have a "fair" rate with a low risk of bias. Regarding Question 5 of the NHLBI tool, none of the included studies justified their sample size. Regarding Question 8, which pertains to exposure, we reported "Not applicable (NA)" for all included studies, as the SBS could neither be classified nor regarded as a continuous variable. The results of the quality assessment are presented in Table 3.4.

Table 3.3 Assessment of risk of bias

Paper	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall
Collins et al. (2005).	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	NR	NA	Y	**Good**
Kelly et al. (2005)	Y	Y	Y	Y	NR	Y	Y	NA	NA	NA	Y	NA	NA	Y	**Good**
Leet et al. (2006)	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	CD	NA	Y	**Good**
Majoor et al. (2017)	Y	Y	Y	Y	N	Y	Y	NA	N	CD	Y	Y	NA	Y	**Good**
Majoor et al. (2018)	Y	Y	Y	Y	N	Y	Y	NA	N	CD	Y	Y	NA	Y	**Good**
Rotman et al. (2018)	Y	Y	Y	Y	NR	Y	Y	NA	N	CD	Y	Y	NA	Y	**Fair**
Meier et al (2022)	Y	Y	Y	Y	CD	Y	Y	NA	Y	N	Y	NA	Y	Y	**Good**

Risk of Bias of the included studies using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Domains: (1) Was this paper's research question or objective clearly stated? (2) Was the study population specified and defined? (3) Was the participation rate of eligible persons at least 50%? (4) Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (5) Was a sample size justification, power description, or variance and effect estimates provided? (6) For the analyses in this paper, where were the exposure(s) of interest measured prior to the outcome(s) being measured? (7) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure or exposure measured as a continuous variable)? (9) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (10) Was the exposure(s) assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was the loss to follow-up after baseline 20% or less? (14) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

3.5 Discussion

This systematic review is the first to synthesise the relationship between SBS and physical outcomes of QoL in patients with FD/MAS. The meta-analysis showed that skeletal burden is negatively associated with the functional ability of FD patients to perform everyday tasks and ambulate independently [5, 22, 25, 26]. The predictive power of SBS suggests that children with scores greater than 30 who walk independently are more likely to experience impaired physical functions in adulthood. Certain endocrinopathies, such as precocious puberty in adults and hyperthyroidism in children, were also found to be associated with high SBS [5, 22]. The included studies demonstrated that FD has a significant negative impact on QoL, particularly in physical health domains.

3.5.1 Comparison of Physical and Mental Health Outcomes

The included studies demonstrated that FD has a significant negative impact on QoL, particularly in physical health domains. Physical health domains, such as physical functions, role physical, bodily pain, and general health scored lower than in the American [25], and Dutch [22, 26] populations. By contrast, the SF-36 social functioning scores were comparable to the American reference standard and only slightly lower than those of the Dutch population. This variation may be attributed to socioeconomic or cultural factors. Furthermore, mental and emotional health appeared to be less affected than physical health. This aspect has yet to be thoroughly investigated in this review, which focused primarily on physical health outcomes. Interestingly, the study by Meier et al. [26]

found that mental health, role emotional, and vitality domains were lower than physical health domains. Meier et al. [26] attributed these findings to the COVID-19 pandemic restrictions during the 2020. Although the full magnitude of the pandemic's impact remains unclear, a systematic review concluded that COVID-19 significantly increased rates of anxiety, depression, post-traumatic stress disorder, and sleep deprivation [33].

3.5.2 Correlation between SBS and HRQoL measures

The physical component of QoL measures was significantly more impaired compared to the mental health component [29]. Although some studies evaluated mental health, correlations with SBS were generally not significant. For example, while the IPQ-R outcome measure demonstrated a relationship with SBS, the UCL coping style tool did not show any significant correlation. This suggests that SBS primarily reflects physical health outcomes rather than mental health aspects. The skeletal burden has also been correlated with other HRQoL measures. In the PODCI questionnaire, the sports and transfer scales correlated positively with lower extremity SBS ($p = 0.02$ and $p = 0.03$, respectively), but not with total SBS [21]. This indicates that FD involvement in the lower extremities affects a child's mobility and participation in physical activities. In contrast, the UCL tool, which focuses on coping strategies, did not capture a relationship with skeletal burden.

3.5.3 Variability in HRQoL tools and the need for disease-specific measures

Variability in the HRQoL tools used across studies further complicates direct comparisons. The SF-36, recommended by international FD/MAS guidelines, was the most used tool. It is a well-validated and widely translated instrument, facilitating its use in diverse populations [31, 32]. However, the lack of FD/MAS-specific QoL tools limits the sensitivity of current instruments in capturing the full impact of the disease. Developing disease-specific measures could provide more accurate insights into the challenges faced by patients and improve clinical care. Not all outcome measures were found to be associated with skeletal burden. The UCL HRQoL tool, which was designed to measure an individual's coping style in adapting to FD/MAS, did not show a significant relationship with SBS [24]. Patients with FD/MAS tend to exhibit more active coping strategies, a heightened propensity to seek social support, and a greater tendency to express emotions compared to individuals with other chronic conditions. Although this HRQoL instrument does not directly measure QoL, it sheds light on the mental, psychological, and social aspects of dealing with FD/MAS. The lack of correlation between SBS and UCL reflects the different purposes of these measures, which is consistent with the absence of a relationship between SBS and the SF-36 mental health domains.

3.6 Limitations

This review has several limitations that must be considered. First, the small sample sizes in the included studies reduce the statistical power and robustness of the findings. Given the rarity of FD/MAS, recruiting large and representative samples is challenging, which affects the reliability of pooled data. Second, most of the included studies were conducted in Western countries, such as the United States and the Netherlands, limiting the generalisability of findings to other populations with different healthcare systems, cultural practices, and socioeconomic conditions. Future research should include larger and more diverse cohorts to ensure broader applicability of results. Third, this review primarily focused on physical health outcomes because SBS is more closely related to functional ability. Mental health outcomes were less frequently reported, leaving the impact of SBS on emotional well-being underexplored. Although some studies assessed mental health, most correlations with SBS were not significant. This highlights the need for future studies to consider both physical and mental health components comprehensively.

Finally, although publication bias was addressed, other forms of bias may have influenced the results. The use of different HRQoL tools across studies may have introduced measurement inconsistencies. While the SF-36 is a widely accepted instrument, other tools measured different outcomes, complicating direct comparisons.

3.7 Conclusion

This systematic review demonstrates that the QoL of patients with FD/MAS, particularly their physical health is significantly lower compared to reference standards. A high SBS is associated with impaired physical function, suggesting its potential as a valuable tool for assessing disease severity. Notably, precocious puberty in adults and hyperthyroidism in children emerged as key factors influencing disease severity. The clinical relevance of SBS lies in its ability to help clinicians classify the degree of FD severity and identify patients at higher risk of functional decline. This early identification enables timely interventions and supports clinicians in managing physical outcomes more effectively. Integrating SBS into routine clinical practice would not only improve disease monitoring but also facilitate personalised management strategies, ultimately enhancing patient care and outcomes.

Future research should focus on validating the SBS in more diverse and larger cohorts to improve its generalisability and predictive accuracy. Longitudinal studies should explore the role of SBS in predicting short-, medium-, and long-term functional outcomes. Additionally, targeted interventions could be developed based on SBS predictions to prevent or minimise disease progression and improve patient quality of life. These steps will ultimately enhance clinical care and guide personalised management strategies needed for patients with FD/MAS.

3.8 References

1. Hartley, I., et al., *Fibrous Dysplasia of Bone and McCune–Albright Syndrome: A Bench to Bedside Review.* Calcif Tissue Int, 2019. **104**(5): p. 517-529.
2. Boyce, A.M. and M.T. Collins, *Fibrous Dysplasia/McCune-Albright Syndrome: A Rare, Mosaic Disease of Gαs Activation.* Endocrine reviews, 2020. **41**(2): p. 345-370.
3. Chapurlat, R.D.M.D.P. and P.M.D.P. Orcel, *Fibrous dysplasia of bone and McCune–Albright syndrome.* Best Pract Res Clin Rheumatol, 2008. **22**(1): p. 55-69.
4. Riddle, N.D. and M.M. Bui, *Fibrous dysplasia.* Arch Pathol Lab Med, 2013. **137**(1): p. 134-138.
5. Collins, M.T., et al., *An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone.* J Bone Miner Res, 2005. **20**(2): p. 219-26.
6. de Castro, L.F., et al., *Activation of RANK/RANKL/OPG Pathway Is Involved in the Pathophysiology of Fibrous Dysplasia and Associated With Disease Burden.* Journal of Bone and Mineral Research, 2018. **34**(2): p. 290-294.
7. Meier, M., et al., *Clinical value of RANKL, OPG, IL-6 and sclerostin as biomarkers for fibrous dysplasia/McCune-Albright syndrome.* Bone, 2023. **171**: p. 116744.
8. Gun, Z.H., et al., *Serum Phosphorus as a Driver of Skeletal Morbidity in Fibrous Dysplasia.* The Journal of Clinical Endocrinology & Metabolism, 2023. **109**(5): p. 1334-1340.
9. Florenzano, P., et al., *Age-Related Changes and Effects of Bisphosphonates on Bone Turnover and Disease Progression in Fibrous Dysplasia of Bone.* Journal of Bone and Mineral Research, 2019. **34**(4): p. 653-660.
10. Szymczuk, V., et al., *Skeletal Disease Acquisition in Fibrous Dysplasia: Natural History and Indicators of Lesion Progression in Children.* Journal of Bone and Mineral Research, 2022. **37**(8): p. 1473-1478.
11. Majoor, B.C., et al., *Outcome of Long-Term Bisphosphonate Therapy in McCune-Albright Syndrome and Polyostotic Fibrous Dysplasia.* Journal of Bone and Mineral Research, 2016. **32**(2): p. 264-276.
12. Berglund, J.A., et al., *Scoliosis in Fibrous Dysplasia/McCune-Albright Syndrome: Factors Associated With Curve Progression and Effects of Bisphosphonates.* Journal of Bone and Mineral Research, 2018. **33**(9): p. 1641-1648.
13. McInnes, M.D.F., et al., *Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement.* JAMA, 2018. **319**(4): p. 388-396.
14. Tools., N.N.S.Q.A. *NHLBI & NIH (2021) Study Quality Assessment Tools.* . [cited 2024; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessmenttools.
15. *The handbook of research synthesis and meta-analysis, 2nd ed*, in *The handbook of research synthesis and meta-analysis, 2nd ed.*, H. Cooper, L.V. Hedges, and J.C. Valentine, Editors. 2009, Russell Sage Foundation: New York, NY, US. p. xvi, 615-xvi, 615.
16. Cumpston, M., et al., *Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions.* Cochrane Database Syst Rev, 2019. **10**(10): p. Ed000142.
17. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* Bmj, 2003. **327**(7414): p. 557-560.
18. Fragkos, K.C., M. Tsagris, and C.C. Frangos, *Publication Bias in Meta-Analysis: Confidence Intervals for Rosenthal's Fail-Safe Number.* Int Sch Res Notices, 2014. **2014**: p. 825383.
19. Cameron, J.I., et al., *Differences in quality of life across renal replacement therapies: A meta-analytic comparison.* American Journal of Kidney Diseases, 2000. **35**(4): p. 629-637.
20. Nair, A.S., *Publication bias - Importance of studies with negative results!* Indian J Anaesth, 2019. **63**(6): p. 505-507.

21. Leet, A.I., et al., *THE CORRELATION OF SPECIFIC ORTHOPAEDIC FEATURES OF POLYOSTOTIC FIBROUS DYSPLASIA WITH FUNCTIONAL OUTCOME SCORES IN CHILDREN.* Journal of bone and joint surgery. American volume, 2006. **88**(4): p. 818-823.
22. Majoor, B.C.J., et al., *Determinants of impaired quality of life in patients with fibrous dysplasia.* Orphanet J Rare Dis, 2017. **12**(1): p. 80-80.
23. Majoor, B.C.J., et al., *Illness Perceptions are Associated with Quality of Life in Patients with Fibrous Dysplasia.* Calcif Tissue Int, 2018. **102**(1): p. 23-31.
24. Rotman, M., et al., *Passive Coping Strategies Are Associated With More Impairment In Quality Of Life In Patients With Fibrous Dysplasia.* Calcif Tissue Int, 2018. **103**(5): p. 469-475.
25. Kelly, M.H., et al., *Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone.* Bone, 2005. **37**(3): p. 388-394.
26. Meier, M.E., et al., *A multidisciplinary care pathway improves quality of life and reduces pain in patients with fibrous dysplasia/McCune-Albright syndrome: a multicenter prospective observational study.* Orphanet Journal of Rare Diseases, 2022. **17**(1): p. 439.
27. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
28. Ware, J.E. and I. New England Medical Center Hospital Health, *SF-36 physical and mental health summary scales : a user's manual*. 1994, Boston: Health Institute, New England Medical Center Boston.
29. Javaid, M.K., et al., *Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome : a consensus statement from the FD/MAS international consortium.* 2019.
30. Ware, J.E., Jr., *SF-36 Health Survey Update.* Spine, 2000. **25**(24).
31. Bullinger, M., et al., *Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International Quality of Life Assessment.* J Clin Epidemiol, 1998. **51**(11): p. 913-23.
32. Wagner, A.K., et al., *Cross-cultural comparisons of the content of SF-36 translations across 10 countries: results from the IQOLA Project. International Quality of Life Assessment.* J Clin Epidemiology, 1998. **51**(11): p. 925-32.
33. Xiong, J., et al., *Impact of COVID-19 pandemic on mental health in the general population: A systematic review.* Journal of Affective Disorders, 2020. **277**: p. 55-64.

Chapter 4:

The Diagnostic Accuracy of Cross-Sectional Imaging Modalities in Fibrous Dysplasia: Systematic Review and Meta-Analysis

4.1 Abstract

Aim

This systematic review aimed to evaluate the diagnostic accuracy of computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy (BS), and positron emission tomography (PET) in diagnosing fibrous dysplasia (FD).

Methods

A systematic search was conducted in PubMed, Google Scholar, Web of Science, and Ovid via Medline databases. Studies assessing the diagnostic performance of cross-sectional imaging modalities in FD diagnosis were included. The methodological quality was evaluated using the QUADAS-2 tool. A bivariate diagnostic meta-analysis was performed to estimate pooled sensitivity and specificity.

Results

Seven studies met the included criteria, with five were included in the meta-analysis. Three included studies used MRI, two studies assessed CT, and two used bone scintigraphy and PET/CT. The pooled sensitivity for MRI was 72.7% (95% confidence interval CI 64.1% to 79.9%) and specificity of 76.8% (95% CI: 69.0% to 83.1%). In contrast, the pooled sensitivity for CT was 90.9% (95% CI: 16.6%–99.8%), and specificity of 84.6% (95% CI: 19.6 to 99.1%). The wide confidence intervals for CT suggest variability across studies, highlighting the need for cautious interpretation.

Conclusion

CT appears to have higher diagnostic accuracy diagnosing FD and differentiating it from other benign and malignant bone tumours, compared to other imaging modalities. However, the substantial variability in sensitivity and specificity estimates, as indicated by wide confidence intervals, limits the robustness of these findings. The small number of included studies and methodological heterogeneity further contribute to uncertainty. Therefore, these results should be interpreted with caution. Further research with larger sample sizes is needed to enhance the reliability of diagnostic accuracy estimates and reduce uncertainty in confidence intervals.

4.2 Introduction

Fibrous dysplasia (FD) accounts for 5-7% of benign bone tumours [1] and is characterised by the presence of abnormal fibrous tissue lesions within bones, which may present as either a single FD lesion or multiple FD lesions. In severe cases, FD can be accompanied by extra-skeletal manifestations, a condition known as McCune-Albright syndrome (MAS). Not all FD lesions are symptomatic; many are discovered incidentally during radiological assessments for unrelated conditions. The radiological appearance of FD lesion is non-specific and can mimic both malignant and benign bone tumours, such as aneurysmal bone cysts, giant cell tumours, non-ossifying fibromas, and osteosarcomas [2]. Metabolic activity and disease progression in FD/MAS are influenced by patient age and the extent of skeletal involvement. The international FD/MAS guidelines identify histopathological analysis of the FD lesion specimens as the gold standard for confirming an FD diagnosis [3]. However, biopsy is often challenging and not always feasible, particularly in cases of extensive FD/MAS involvement or when lesions are located in anatomically difficult regions. In the context of the studies included in this systematic review, not all utilised histopathology as the reference standard. Some studies relied on a combination of diagnostic criteria, including genetic analysis of mutations in the alpha subunit of the G protein (GNAS) gene and radiological follow-up to confirm FD diagnoses. Other diagnostic approaches include clinical assessment of bone turnover markers, genetic analysis of mutations in the alpha subunit of the G protein (*GNAS*) gene, and cross-sectional imaging of the skeleton [4].

The assessment of bone turnover markers is highly influenced by age, and bisphosphonates treatment, rendering them unsuitable as a sole diagnostic tool for FD/MAS. Similarly, genetic testing for the presence of *GNAS* mutations is not always definitive in confirming FD/MAS disease. Cross-sectional imaging modalities, including conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy (BS), single-photon emission computed tomography (SPECT), and positron emission tomography (PET), play a crucial role in the diagnostic, management and treatment of FD/MAS. These imaging modalities provide essential anatomical and physiological insights that assist clinicians in distinguishing FD form other benign and malignant bone tumours, monitoring disease progression, and planning surgical interventions.

Each imaging modality has distinct advantages and limitations in diagnosing FD. Conventional radiography is often the first line imaging modality, revealing the characteristic "ground glass" appearance of FD lesions; however, it lacks sensitivity in detecting early-stage or deeply located lesions. often observed in conventional radiographs, CT scans, and sometimes MRI [5]. CT offers superior spatial resolution, enabling detailed assessment of cortical bone changes and lesion characteristics, making it particularly useful for evaluating craniofacial FD. MRI provides excellent soft-tissue contrast and can differentiate FD from other disease, although FD lesions may exhibit variable signal intensities due to difference in fibrous tissue composition. Nuclear medicine bone scintigraphy and SPECT are valuable for detecting polyostotic FD by identifying area of increased bone turnover, yet the lack specificity in differentiating FD from other metabolic or neoplastic bone disease.

In PET, particularly 18F-FDG PET/CT, can offer metabolic insights that may assist in distinguishing FD from other abnormalities by measuring the lesion uptake of FDG. Despite the availability of multiple imaging modalities, no gold-standard imaging modality exists for diagnosing FD. The selection of imaging modality is typically guided by clinical complications, lesion location, and the extent of FD involvement. However, the diagnostic accuracy of these imaging modalities has not been comprehensively evaluated, leading to variability in clinical practice and limiting the standardisation of FD management.

In this review, we considered studies that employed histopathology, genetic testing, or radiological confirmation as reference standards to reflect the diverse clinical practices in diagnosing FD. This systematic review aims to address a critical gap in the literature by evaluating the available studies focused on assessing the diagnostic accuracy of various imaging modalities in detecting and differentiating FD/MAS from other benign bone tumours.

4.3 Materials and Methods

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42024503994) and was reported according to the referred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) guidelines. Ethical approval was not required for this systematic review and meta-analysis, as it involved the analysis of data from previously published studies and did not include any new data collection from human participants.

The research question was developed using (population, intervention, comparison, outcome) (PICO) framework, as followed:

- (P) population: children and adults with FD/MAS.
- intervention: index tests (CT, MRI, orthopantomogram, PET, radiograph, and bone scintigraphy).
- (C) compare: reference standards (biopsy, genetic testing, other imaging modalities).
- (O) Outcome: diagnostic accuracy (sensitivity and specificity, predictive values, likelihood ratios and observer reliability).

The research question addressed was: “What is the diagnostic accuracy of cross-sectional medical imaging modalities for the diagnosis of FD?”. A comprehensive electronic search of databases for papers published from 1990 to March 2024 focused on the diagnostic accuracy or assessment of FD/MAS using different imaging modalities. The databases included PubMed, Google Scholar, Web of Science, and Ovid via Medline for papers published in peer-reviewed journals.

A manual search of the reference lists of the included papers may have been missed during the electronic search. Table 4.1 summarises the keywords. The search was conducted by a single reviewer (Arwa Alhulwah, AA). Two reviewers (AA) and (Prof. Amaka C. Offiah, ACO) independently screened the titles and abstracts. One reviewer (AA) assessed the eligibility of the full-text papers, which was then independently verified by a second reviewer (ACO). Disagreements and discrepancies were resolved through discussion.

4.3.1 Data extraction

One reviewer (AA) performed data extraction using a standardised table of the following data: authors and year or publication, study design, sample size, number of patients with FD/MAS, FD subtype, reference standard, type of imaging modality, and main findings.

Table 4.1 Search terms

Boolean operators	Search terms
	"Fibrous dysplasia" OR "McCune-Albright syndrome" OR "FD" OR "MAS" OR "FD/MAS"
AND	"Magnetic resonance imaging" OR "MRI" OR "computed tomography" OR "CT" OR "Positron emission tomography" OR "PET" OR "single photon emission tomography" OR "SPECT" OR "radiography" OR "x-ray" OR "scintigraphy" OR "radionuclide imaging" OR "orthopantomogram" OR "OPG"
AND	"Diagnostic accuracy" OR "sensitivity" OR "specificity" OR "predictive value" OR "PPV" OR "NPV" OR "observer reliability" OR "odd ratio" OR "receiver operating characteristic curve" OR "ROC curve"

4.3.2 Eligibility criteria

The inclusion criteria for papers eligible for this systematic review required that studies be original research involving patients with fibrous dysplasia/McCune-Albright syndrome (FD/MAS) and include a clear reference standard to confirm the diagnosis. Additionally, eligible studies had to utilise one or more imaging modalities, such as CT, MRI, orthopantomogram, PET, radiography, or SPECT, and assess the diagnostic accuracy of FD. Only full-text articles written in English were considered. Studies were excluded if they were non-human research or focused on treatment, surgical outcomes, or the use of the skeletal burden score. Furthermore, case reports, review articles, observational studies, abstracts, and conference reports were not included in the review.

4.3.3 Statistical methods

4.3.3.1 Quantitative analysis (meta-analysis)

The sensitivity, specificity and (95% confidence intervals (CI)) of the index tests were assessed based on the extracted raw data on the diagnostic values (true positive values (TPV), false positive values (FPV), true negative values (TNV), false negative values (FNV), positive predictive value (PPV), and negative predictive value (NPV)). Sensitivity refers to the proportion of individuals diagnosed with FD who tested positive in the index tests (TP/TP+FN). Specificity refers to the proportion of individuals not diagnosed with FD who tested negative in the index tests (TN/TN+FP) [6]. The meta-analysis involved a bivariate diagnostic random-effects approach to evaluate the diagnostic accuracy of cross-sectional imaging modalities [27]. This approach was chosen for its ability to jointly estimate the sensitivity and specificity. Diagnostic accuracy values, including sensitivity and specificity, were calculated for each study and logit transformations. Logit

transformations stabilise variances, which is critical because raw proportions may have variance depending on the proportion, potentially leading to skewed results in meta-analysis. The variance components between studies were also assessed to evaluate heterogeneity. Heterogeneity was quantified using Restricted Maximum Likelihood (REML) estimation method, which provided robust estimates of between-study variance. Moreover, a variance-covariance structure was implemented to account for study-level heterogeneity and clustering effects.

Diagnostic accuracy was graphically illustrated using Receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) was used as a summary measure of discriminative performance of an index test. The AUC values range from 0 meaning has a poor discriminative performance, whist 1 meaning excellent discriminative performance between disease and non-disease. Furthermore, the Summary Operating Receiver Curve (SORC) is a recently presented tool used to evaluate the pooled sensitivity and specificity values for each index test across multiple studies [7].

The SROC allowed a consolidated view of the diagnostic performance across studies [8]. It plots sensitivity against the false positive rate (1-specificity) to provide a consolidated view of diagnostic performance. The meta-analysis was conducted by two independent reviewers (AA and FS) to ensure reliability. Meta-analyses were performed using the metafor package R (version 4.4.1), while RevMan 5 and SAS (version 9.2) were used for statistical analyses and diagnostic accuracy plots and graphs.

4.3.3.2 Qualitative assessment

The quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2) [9]. QUADAS-2 is a tool consists of four domains: patient selection, index test, reference standard, and study flow and timing. The risk of bias is assessed for each domain and the applicability of a study is assessed for patient selection, index test and reference standard domains. Each domain is assessed in terms of risk of bias. All three reviewers (AA, ACO and AS) assessed the risk of bias of the included studies independently.

4.4 Results

4.4.1 Literature search

The initial search yielded 21,007 papers, of which 2,660 duplicates were removed. In total, 17,787 titles and abstracts were screened for eligibility. The full text of 836 papers were retrieved for review; 433 papers were screened against the inclusion and exclusion criteria. Seven papers fulfilled the inclusion criteria of which, five studies were included in the meta-analysis. The search process followed the PRISMA guidelines, and the corresponding steps and search results are summarised in the PRISMA flowchart Figure 4.1. The characteristics of the included studies are summarised in Table 4.2. Of the seven included studies, four were retrospective in design [10 19], and three were prospective studies. Three studies were conducted in the United States of America (USA), two in Turkey, and the remaining were from Germany, and China. Three studies assessed the diagnostic accuracy of MRI, two assessed CT, and one each assessed PET/CT, and bone scintigraphy.

4.4.2 Gold standard

All the included papers reported histopathological analysis of the biopsied FD lesion as the preferred gold standard for confirming the diagnosis of FD. Other gold standards used in the included studies were one-year follow-up of radiological imaging (CT or MRI) by monitoring disease progression [16], or genetic analysis of the presence of *GNAS* mutation within the lesion [17].

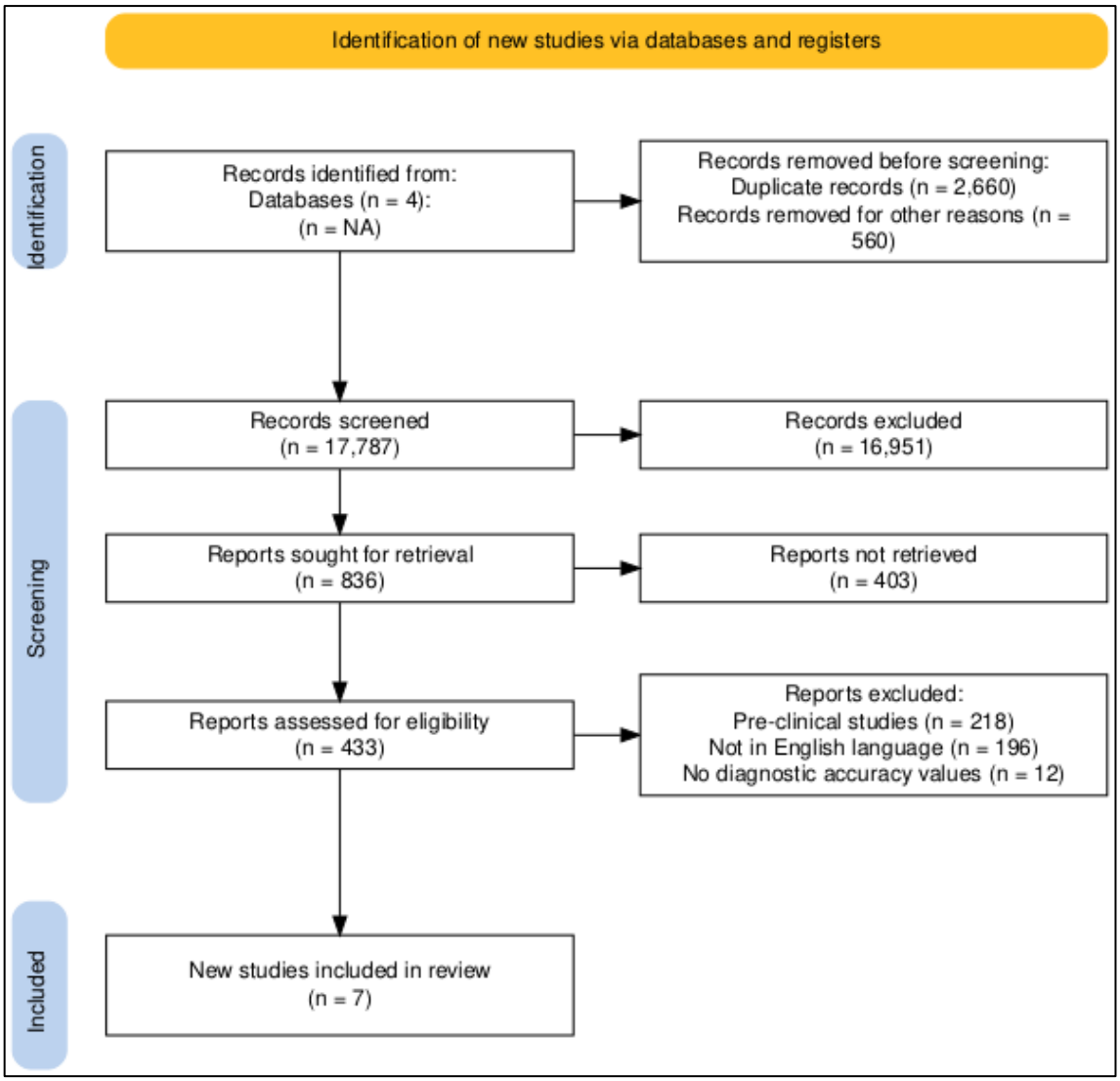


Figure 4.1 PRISMA flowchart

Table 4.2 Characteristics of the included studies

Author, year	Country	Study design	Sample size	Number of FD patients	Location of FD lesions	Mean age, (age range)	Male (%)	Reference standard	Index test
Ahlawat, 2015 [16]	USA	Retrospective	31	2	Femur, tibia	37.2, (4-80)	48.3	Histopathological	MRI
Efune, 2011 [14]	USA	Retrospective	60	11	Craniofacial bones	42.3, (8-76)	43.3	Histopathological	CT
Gephart, 2011[13]	USA	Retrospective	51	5	Craniofacial bones	N/A	N/A	Histopathological	CT
Kim, 2019 [17]	Germany	Retrospective	32	32	Craniofacial bones	41.5, (6-80)	34.3	Genetic analysis, Histopathological, CT	MRI
Ones, 2012 [18]	Turkey	Prospective	12	12	Lower and upper extremities, mandible, femur	38, (12-73)	50	Histopathological	BS using ^{99m}Tc-MDP and ^{99m}TcMIBI
Pekcevik, 2013 [15]	Turkey	Prospective	26	1	Femur	34.5, (8-76)	57.6	Histopathological	MRI
Tian, 2009 [16]	China	Prospective	67	10	N/A	46, (9-76)	68.6	Histopathological and radiological follow-up	PET/CT

BS, bone scintigraphy; CT, computed tomography; FD, fibrous dysplasia; MDP, methylene diphosphonate: MIBI, hexakis-2-methoxyisobutylisonitrile; MRI, magnetic resonance imaging; PET, positron emission tomography; USA, United States of America.

4.4.2.1 Methodological quality

Table 4.3 summarises the quality assessment of the included papers. High risk of bias in patient selection and reference standard was reported for Ones et al. [18] and Kim et al. [17] due to the lack of clarity on whether the patients were selected consecutively or through random sampling. Five studies exhibited an unclear risk of bias in the reference standard because it was not specified if the biopsy was taken with or without knowledge of the index test results, and no diagnostic threshold was provided in these papers. Two studies had an unclear risk of bias for the index test due to the ambiguity surrounding whether the index test results were interpreted without knowledge of the reference standard findings.

Table 4.3 Quality assessment of diagnostic accuracy studies (QUADAS-2) tool of the included studies

Study	Modality	Patient selection	Index test	Reference standard	Flow and Timing	Patient Selection	Index test	Reference standard
Ahlawat et al. [16]	MRI	Low	Unclear	Unclear	Low	Low	Low	Low
Efune et al. [14]	CT	Unclear	Low	Unclear	Low	Low	Low	Low
Gephart et al. [13]	CT	Low	Unclear	Low	Low	Low	Low	Low
Kim et al. [17]	MRI	High	Low	Unclear	Low	Low	Low	Low
Ones et al. [18]	BS	Low	High	High	Low	Low	Low	Low
Pekcevik et al. [15]	MRI	Low	Low	Unclear	Low	Low	Low	Low
Tian et al. [16]	PET	Low	Low	Unclear	Low	Low	Low	Low

4.4.3 Studies included for the meta-analysis

Five studies were included in this meta-analysis [13-15, 17, 19]. Three studies investigated the diagnostic accuracy of MRI in a total of 89 patients [15, 17, 19]. Two studies investigated the diagnostic accuracy of CT in 111 patients [13, 14]. All studies measured the diagnostic accuracy of MRI and CT in differentiating benign from malignant bone tumours. However, one study included a patient cohort with craniofacial FD to assess the diagnostic accuracy and characteristics of FD lesions.

4.4.3.1 MRI diagnostic accuracy

Table 4.4 summarise the measured specificity and sensitivity of MRI. The results of the meta-analysis indicated that MRI exhibited an overall sensitivity of 0.727 (95% CI: 0.641–0.799), and an overall specificity of 0.768 (95% CI: 0.690–0.831) for diagnosing fibrous dysplasia (Figure 4.2 and 4.3) [15, 17, 19].

The I^2 statistic for heterogeneity was negligible (0.001%), suggesting a low between study variability. The AIC was -11.317, and the BIC was -9.804, indicating a good fit for the model. The AUC for the summary receiver operating characteristic ROC curve was 0.777, with a partial AUC (restricted to observed false positive rates and normalised) of 0.694 (Figure 4.4). The I^2 estimates using different approaches ranged from 0% to 1.8%–38.7% [20] [16], reflecting minimal to moderate heterogeneity. Overall, the results demonstrated that MRI has substantial diagnostic accuracy for FD, with MRI showing slightly higher sensitivity and specificity. Low heterogeneity across studies supports the robustness of these findings.

Table 4.4 Overall diagnostic accuracy of magnetic resonance imaging (MRI)

Metric	Overall values (95% CI)	I^2
Sensitivity	**0.727** [0.641 - 0.799]	.001%
Specificity	**0.768** [0.690- 0.831]	.001%
AUC	**0.694**	
SORC	**0.777**	
AIC	**-11.37**	
BIC	**-9.80**	
I^2 estimates	Zhou and Dendukuri approach: **0 %** Holling sample size unadjusted approaches: **33.8 - 38.7 %** Holling sample size adjusted approaches: **1.8 - 2.3 %**	

Abbreviations: AIC,akaike information criterion; AUC, area under the curve; BIC, Bayesian information criterion; CI, confidence interval; SORC, summary receiver operating characteristic.

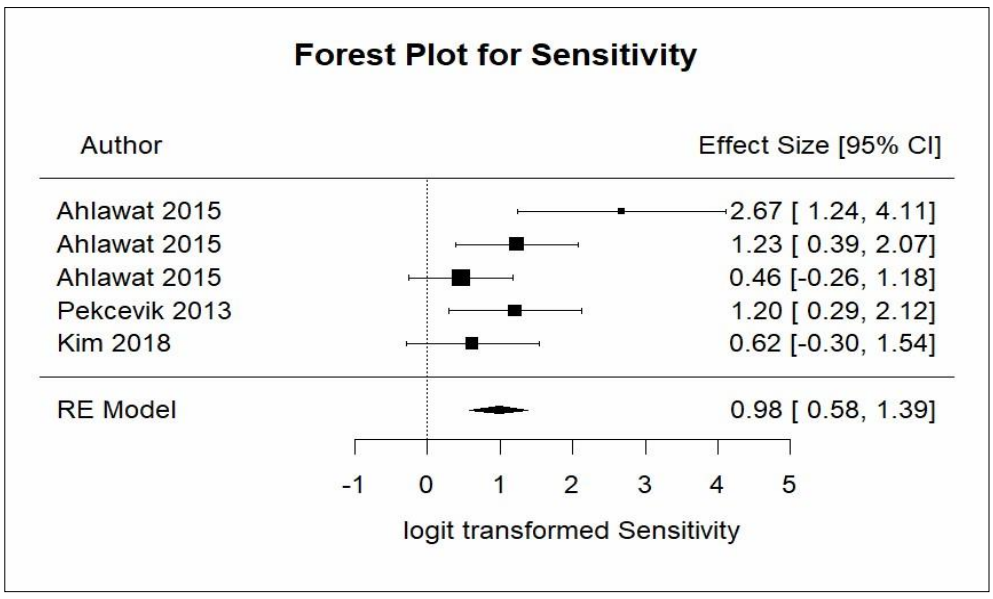


Figure 4.2 Forest plot for logit transformed sensitivity of MRI

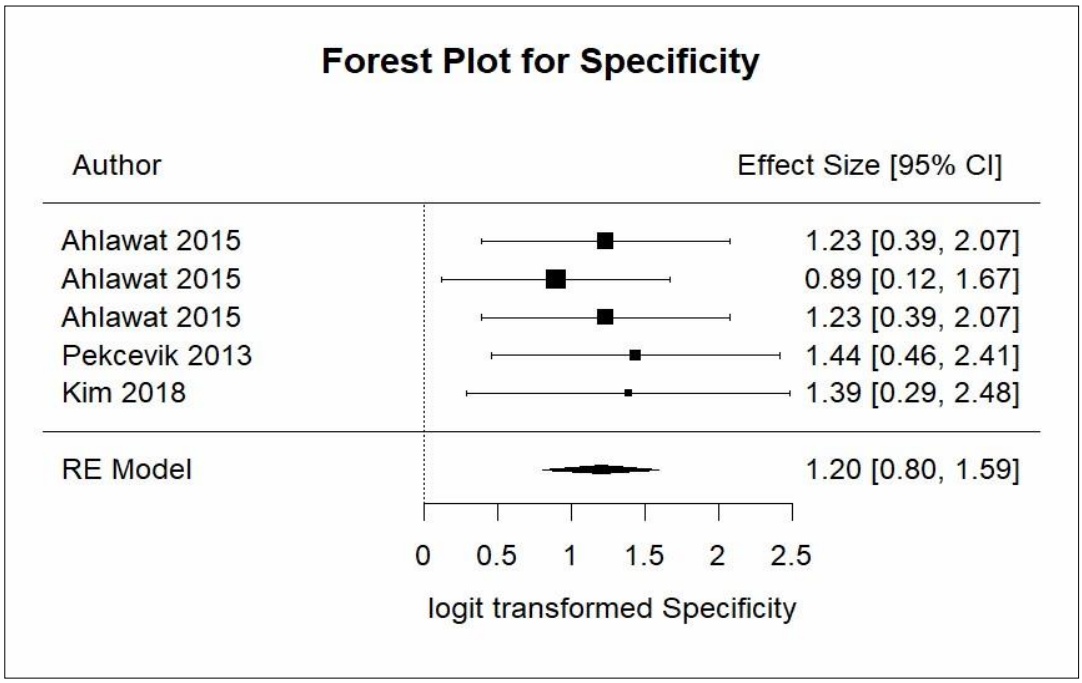


Figure 4.3 Forest plot of logit transformed specificity of MRI

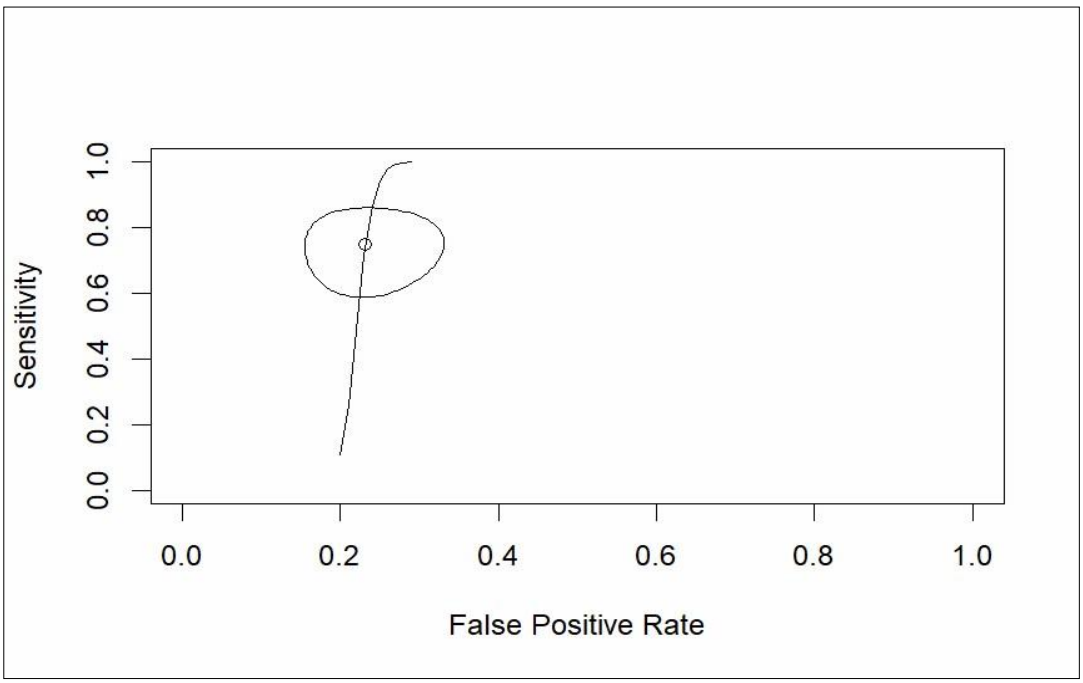


Figure 4.4 SORC for MRI accuracy

Summary Operating Receiver Curve (SORC) for magnetic resonance imaging (MRI) illustrating the diagnostic performance in detecting fibrous dysplasia (FD). The curve represents the relationship between sensitivity and the false positive rate, with the ellipse indicating the confidence region around the summary point estimate. SORC, Summary Operating Receiver Curve; MRI, magnetic resonance imaging.

4.4.3.2 CT diagnostic accuracy

The results, given in Table 4.4 and Figure 4.5 and 4.6 for CT in diagnosing FD indicate high overall performance. The meta-analysis showed that CT had an overall sensitivity of 0.909 (95% CI: 0.166–0.998) and an overall specificity of 0.846 (95% CI: 0.196–0.991) [13, 14]. These results suggest that CT is highly effective in correctly identifying FD cases (high sensitivity), as well as in correctly excluding non-FD cases (high specificity). The analysis also considers various measures of model fit and heterogeneity. The AIC was -6.921, and BIC was -7.963, indicating a good fit for the model. As shown in Figure 4.7, the AUC for the SROC curve was 0.942, and the partial AUC, restricted to observed false-positive rates and normalised, was 0.938, both reflecting excellent diagnostic ability (Table 4.5).

Heterogeneity among studies was assessed using the I^2 statistic, which showed significant variability. The overall I^2 estimates were 89.76% for sensitivity and 96.18% for specificity, suggesting substantial between-study variability.Overall, these findings demonstrate that CT has substantial diagnostic accuracy for FD, with high sensitivity and specificity values, although there is notable heterogeneity across studies (Figure 4.5). The low sensitivity reported in Efune et al. (2012) may be due to a heterogeneous nature of the FD lesions, radiological and histopathological discordance, and the presence of indeterminate cases that required histopathological confirmation for accurate diagnosis. Additionally, overlapping imaging characteristics of fibrous dysplasia and ossifying fibroma likely contributed to diagnostic uncertainty.

Table 4.5 Overall diagnostic accuracy of computed tomography (CT)

Metric	Overall values [95% CI]	I^2
Sensitivity	**0.909** [0.166 - 0.998]	89.76%
Specificity	**0.846** [0.196 - 0.991]	96.18%
AUC	**0.942**	
SORC	**0.938**	
AIC	**- 6.921**	
BIC	**- 7.963**	
I^2 estimates	Zhou and Dendukuri approach: **50.4 %** Holling sample size unadjusted approaches: **70 - 93.9%** Holling sample size adjusted approaches: **4.3 - 20.4%**	

Abbreviations: AIC, akaike information criterion; AUC, area under the curve; BIC, bayesian information criterion; CI, confidence interval; SORC, summary receiver operating characteristic.

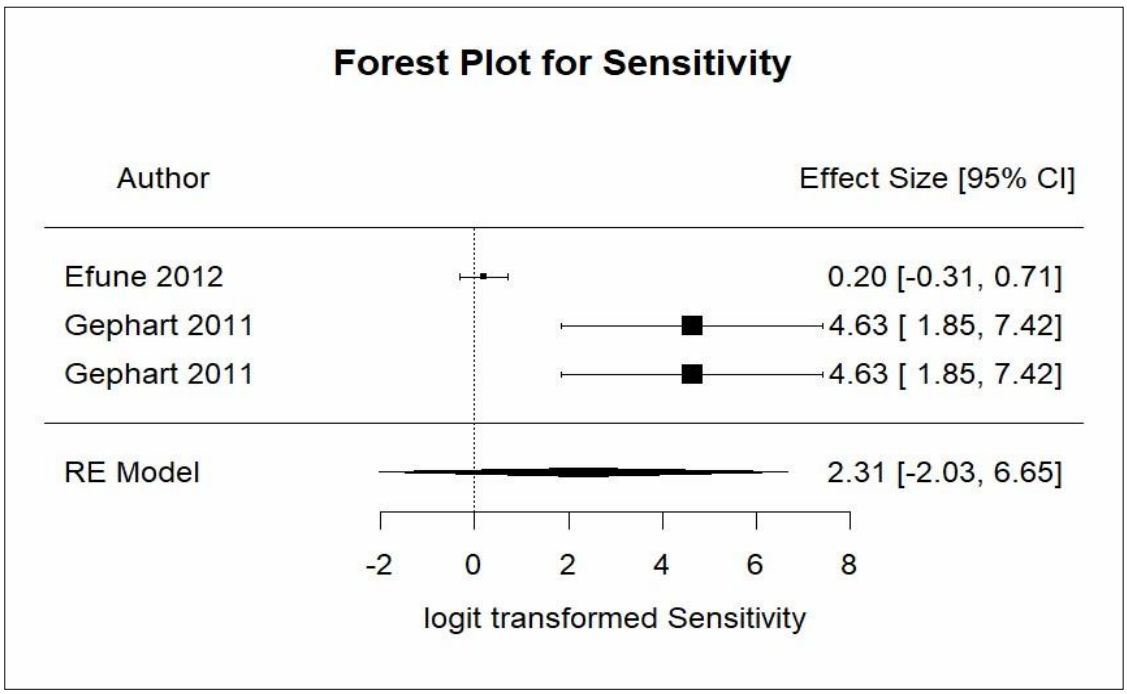


Figure 4.5 Forest plot for logit transformed sensitivity of CT

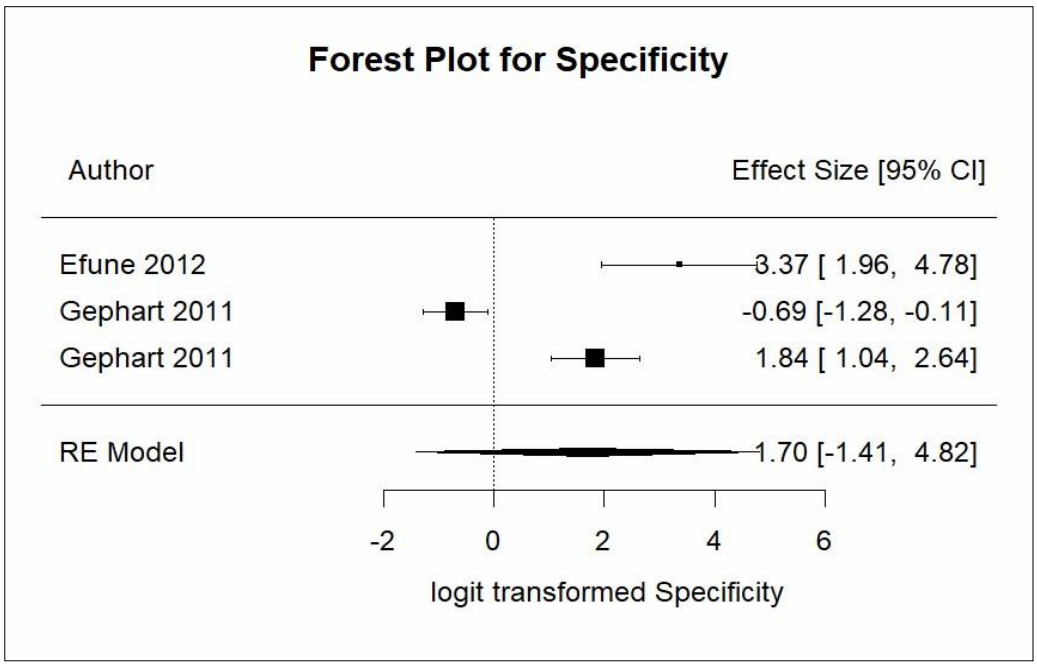


Figure 4.6 Forest plot for logit transformed sensitivity of CT

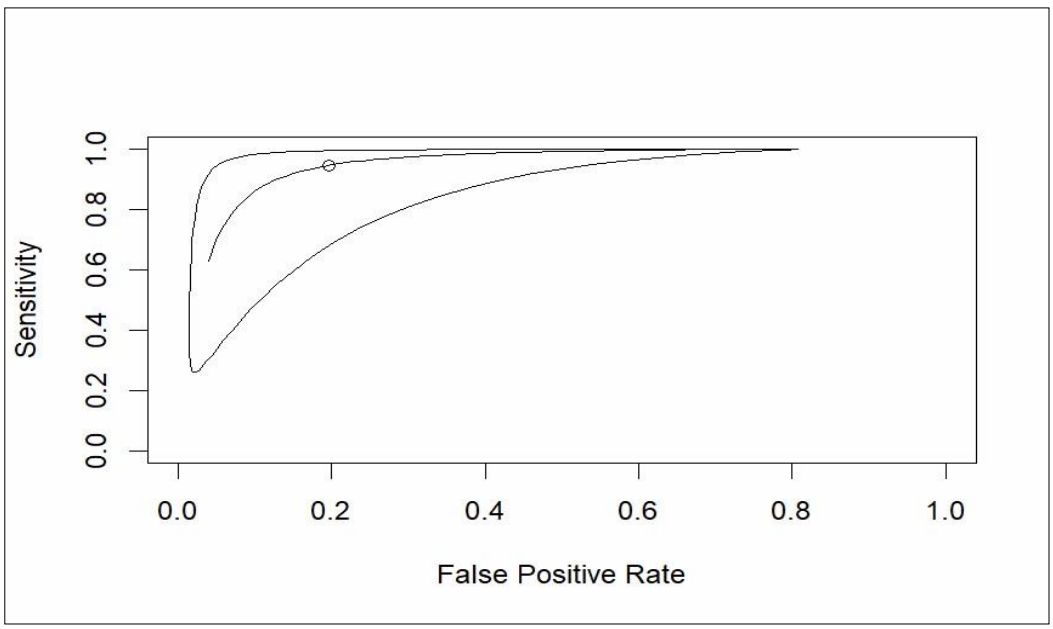


Figure 4.7 SORC for CT accuracy

Summary Operating Receiver Curve (SORC) for magnetic resonance imaging (MRI) illustrating the diagnostic performance in detecting fibrous dysplasia (FD). The curve represents the relationship between sensitivity and the false positive rate, with the ellipse indicating the confidence region around the summary point estimate. SORC, Summary Operating Receiver Curve; MRI, magnetic resonance imaging.

4.5 Discussion

The purpose of this review was to systematically evaluate the literature regarding the diagnostic accuracy of various imaging modalities to diagnosing FD in the absence of gold standard. The wide clinical spectrum of FD makes it variable from a case to another. Therefore, the choice of appropriate radiological modalities depends on the extent of FD and the location of FD involvement in the skeleton. The appearance of FD on radiological imaging is heterogeneous. The international FD/MAS guidelines describe the characteristic FD appearance depending on the location of the lesion, and the type of imaging modalities used [5]. The most common anatomical locations of FD lesions reported by the included studies were the craniofacial bones and femur. Craniofacial involvement is common in PFD in about 50% of cases and 25% cases of MFD FD involvement of the femur is more common in PFD with almost 90% of the cases [Feller, 2009]. Our meta-analysis demonstrated that CT is superior to MRI in detecting FD lesions, with a pooled sensitivity of 90.9 %, a pooled specificity of 84.6 %, and a SROC curve of 0.942. The high diagnostic accuracy of CT in diagnosing and differentiating FD from other bone tumours in the skull, can be attributed to its superior spatial resolution, which effectively highlights characteristic features such as ground glass-opacity, radiolucency, and cortical thinning.

However, when interpreting these findings, it is important to consider the observed wide CI associated with the sensitivity and specificity estimates, particularly in studies with small sample sizes. Wide CI indicate a great degree of heterogeneity and variability in study results. The observed heterogeneity in two included studies should be carefully considered when interpreting the diagnostic accuracy of CT. Heterogeneity in meta-analyses can arise from clinical, methodological, or statistical

differences [22]. In this study, potential sources of heterogeneity may include variations in study populations, such as differences in patient age, FD severity, and lesion location. Moreover, discrepancies in imaging protocol such as imaging parameters, image acquisition settings could contribute to the variability on diagnostic performance which are not mentioned by the authors of the included papers. Furthermore, the definition of a accurate FD diagnosis varied across studies, confirmed by histopathological confirmation, while few papers used radiological follow-up which adding another layer of inconsistency.

The international FD/MAS guidelines recommended the use of CT in staging craniofacial FD. Moreover, the thin slice thickness of CT images is widely used in pre-operative imaging of the skull, proximal femur, pelvis and spine. However, CT imaging is associated with exposure to ionising radiation, of approximately 2.1 mSv, equivalent to 30 series of radiographs [23]. Three studies used MRI to differentiate malignant from benign bone tumours in children and adults of which two studies assessed the ADC values of the ROI. The value of ADC reflects the cellularity within the lesion. The FD finding on MRI are generally non-specific, depending on the amount of cystic, trabecular, fatty tissue, cellularity, and cartilage within the lesion. Thus, the appearance of FD lesion varies in T1- and T2-weighted imaging. Furthermore, craniofacial FD lesions were generally heterogeneous under MRI. Craniofacial FD lesions tend to be hypointense on T1weighted MRI images. The classical ground glass appearance is not seen in all FD lesions under MRI. However, 97% of craniofacial FD lesions showed ground glass appearance on T1- , and T2-weighted images and contrast enhancement images [17]. One study described the craniofacial FD lesion appearance on MRI, with 93.9% cortex thinning, 44.4% homogeneous density on T1- and 38.9% on T2-

weighted. Almost all CFD had contrast enhancement. About 58.39% were hypointense on T1-weighted images, with an accuracy 56 %, and 77.8% were hyperintense intensity on T2-weighted images with an accuracy 71%. Compared with CT, 97% of craniofacial FD lesions had the classical ground glass appearance with accuracy of 95%. Generally, the appearance of FD on T1- and T2-weighted images have different intensities; in T1- the intensity is low to intermediate, and T2-weighted images, intermediate to high enhancement. However, the amount of fibrous tissue, cystic components, and vascularity within the lesion can alter the appearance of FD on T1- and T2-weighted images. Due to the non-specific appearance of FD, a disease confirmation such as histopathological testing of the lesion and CT imaging genetic to confirm the MRI findings.

Pekecivk et al [15] found that ADC values of benign tumour are greater than those of malignant tumours by 1 ADC value. One patient diagnosed with FD had a mean minimum ADC value of 1.41x $x10^{-3}$ mm^2/s, the lowest among the benign ADC tumour values. Conversely, bone cyst had the highest ADC values among benign bone tumours. There is some overlap in ADC value between benign and malignant tumours, as mentioned by the authors. Similarly, Ahalwat et al. [16] also used DWI-MRI to differentiate benign and malignant bone tumours. Two patients diagnosed with FD had mean minimum ADC values of 1.2 and 1.4 $x10^{-3}$ mm^2/s, which were lower than ADC values of bone cyst.

Other imaging modalities included in this review are bone scintigraphy and ^{18}F-FDG PET/CT. A study by Ones et al [18] compared the findings of FD on ^{99m}Tc-MDP compared with ^{99m}Tc-MIBI scintigraphy in 12 patients with 43 FD lesions. Patients with clinical symptoms such as pain and swelling around the lesion showed increased uptake on

MIBI compared with MDP. ^{99m}Tc-MIBI demonstrated 100% sensitivity in both early and late phase imaging, whereas the specificity was 93% for the early phase and 98% for the late phase when compared to MDP.

Another recommendation of the international FD/MAS guidelines is the use of radionuclide bone scintigraphy to assess FD involvement within the skeleton [5]. The use of ^{99m}Tc-MDP is common when suspecting polyostotic FD. On the other hand, ^{99m}Tc-MIBI, known for cardiac imaging provides promising correlation between the presented FD clinical complications and FD involvement compared with MDP which there were no differentiation between the foci uptake of asymptomatic to symptomatic FD lesion. ^{99m}Tc-MIBI bone scintigraphy is performed in two phases: early phase, immediately after radiopharmaceutical injection, and the late phase, approximately two hours after the administration of ^{99m}Tc-MIBI. The sensitivity and specificity of ^{99m}Tc-MIBI were superior to ^{99m}Tc-MDP bone scintigraphy. One study quantified the ^{99m}Tc-MIBI uptake by calculating the ROI of the foci uptake of the lesion and dividing it by the uptake of the bilateral area. No to mild uptake of the ^{99m}Tc-MIBI bone scintigraphy in the early phase was seen in benign tumours compared to malignant tumours which had moderate to severe uptake. The accuracy of ^{99m}Tc-MIBI was 83.05% compared to histopathological analysis of the biopsy [18]. No single imaging modality can be definitively regarded as the gold standard for diagnosing FD. The broad spectrum of manifestations, the diverse features of FD across different imaging modalities, and the resemblance of FD lesions to other benign and malignant bone tumours make it challenging to rely solely on radiological findings. Accurate diagnosis often requires corroboration through additional radiological assessments or histopathological analysis of a lesion biopsy.

4.5.1 Limitations

This study has several limitations. Firstly, the limited number of included studies affected the robustness of the meta-analysis and the strength of the review findings. Furthermore, a formal assessment of publication bias was not feasible due to the small number of included studies. The assessment of publication bias by Egger's test or funnel plots requires a minimum of 10 studies for meaningful interpretation [18]. Secondly, the heterogeneity in the methodologies of the included studies means that the findings should be interpreted with caution. Thirdly, we could not assess the diagnostic accuracy of bone scintigraphy and PET due to the limited number of the included papers that employed these imaging modalities. Fourthly, four of the included papers were retrospective, introducing potential retrospective bias, while three were prospective. Lastly, the study by Ones et al [18] dates to 2009, and technical advancements in PET/CT imaging may have improved diagnostic capabilities. Furthermore, future studies should provide a comprehensive dataset of diagnostic, potentially impacting the generalisability of the findings.

4.6 Conclusion

Our systematic review suggests that CT may offer higher diagnostic accuracy for FD compared to MRI, as indicated by its superior sensitivity and specificity. However, these findings should be interpreted with caution due to the limited number of studies, potential methodological heterogeneity, and retrospective bias present in some of the included studies. Moreover, no single imaging modality can be definitively regarded as the gold standard for the diagnosis of FD, as each has its inherent limitations. Therefore, histopathological or radiological confirmation remains essential for accurate diagnosis, particularly given the potential for FD to mimic other benign and malignant bone tumours.

Further large-scale, prospective studies with larger sample size and standardised methodologies are needed to validate these findings and establish more robust diagnostic guidelines. Such studies should aim to reduce heterogeneity, incorporate technological advancements, and provide comprehensive diagnostic accuracy data to enhance the current evidence base for FD imaging.

4.7 References

1. DiCaprio MR, Enneking WF. Fibrous Dysplasia: Pathophysiology, Evaluation, and Treatment. JBJS. 2005; 87(8).
2. Riddle ND, Bui MM. Fibrous Dysplasia. Archives of Pathology & Laboratory Medicine. 2013; 137(1):134-138.
3. Javaid MK, Boyce A, Appelman-Dijkstra N, Ong J, Defabianis P, Offiah A, et al. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis. 2019; 14(1):139.
4. Spencer T, Pan KS, Collins MT, Boyce AM. The Clinical Spectrum of McCune-Albright Syndrome and Its Management. Horm Res Paediatr. 2019; 92(6):347-356.
5. Chapurlat RD, Orcel P. Fibrous dysplasia of bone and McCune-Albright syndrome. Best Pract Res Clin Rheumatol. 2008; 22(1):55-69.
6. Campbell JM, Klugar M, Ding S, Carmody DP, Hakonsen SJ, Jadotte YT, et al. Diagnostic test accuracy: methods for systematic review and meta-analysis. JBI Evidence Implementation. 2015; 13(3).
7. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005; 58(10):982-990.
8. Jones CM, Athanasiou T. Summary Receiver Operating Characteristic Curve Analysis Techniques in the Evaluation of Diagnostic Tests. The Annals of Thoracic Surgery. 2005; 79(1):16-20.
9. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011; 155(8):529-536.
10. Gephart MGH, Colglazier E, Paulk KL, Vogel H, Guzman R, Edwards MSB. Primary Pediatric Skull Tumors. PEDIATRIC NEUROSURGERY. 2011; 47(3):198-203.
11. Efune G, Perez CL, Tong L, Rihani J, Batra PS. Paranasal sinus and skull base fibroosseous lesions: When is biopsy indicated for diagnosis? International Forum of Allergy and Rhinology. 2012; 2(2):160-165.
12. Pekcevik Y, Kahya M, Kaya A. Diffusion-weighted magnetic resonance imaging in the diagnosis of bone tumors: Preliminary results. Journal of Clinical Imaging Science. 2013; 3(1).
13. Kim D, Heetfeld A, Steffen IG, Hermann KGA, Hamm B, Elgeti T. Magnetic resonance imaging features of craniofacial fibrous dysplasia. Polish Journal of Radiology. 2019; 84:e16-e24.
14. Ones T, Erol B, Aras M, Dede F, Erdil TY, Inanir S, et al. The role of dual-phase Tc-99m MIBI in the evaluation of potentially operable lesions detected by bone scanning in fibrous dysplasia: A long-term prospective follow-up study. Nuclear Medicine Communications. 2012; 33(3):288-296.
15. Ahlawat S, Khandheria P, Subhawong TK, Fayad LM. Differentiation of benign and malignant skeletal lesions with quantitative diffusion weighted MRI at 3 T. European Journal of Radiology. 2015; 84(6):1091-1097.
16. Tian, R., Su, M., Tian, Y. et al. Dual-time point PET/CT with F-18 FDG for the differentiation of malignant and benign bone lesions. Skeletal Radiol 38, 451–458 (2009). https://doi.org/10.1007/s00256-008-0643-0.
17. Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230
18. Cleeland C, Ryan K. Pain assessment: global use of the Brief Pain Inventory. Annals of the Academy of Medicine, Singapore. 1994; 23(2):129-138.
19. Feller, L., Wood, N.H., Khammissa, R.A. *et al.* The nature of fibrous dysplasia. *Head Face Med* **5**, 22 (2009). https://doi.org/10.1186/1746-160X-5-22
20. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119–1129. doi: 10.1016/s0895-4356(00)00242-0

Chapter 5:

Clinicians' Knowledge and Use of Skeletal Burden Score in Fibrous Dysplasia: An International Survey

5.1 Abstract

Aim

In 2019, the international fibrous dysplasia/McCune-Albright syndrome (FD/MAS) guidelines recommended the use of skeletal burden score (SBS) when evaluating the FD skeletal involvement. We attempt to capture the knowledge and use of the SBS when diagnosing FD amongst clinicians worldwide.

Methods

An anonymous, online survey was designed and distributed to the members of the European Society of Paediatric Radiology (ESPR) musculoskeletal taskforce, the Saudi Commission for Health Specialties (SCFHS), and the British Paediatric and Adolescent Bone Group (BPABG). The survey contained ten (three open- and seven close-ended) questions. The survey link was circulated twice starting from 28th February,2022 and was closed on 30th July 2022.

Results

A total of 59 responses were obtained from clinicians across diverse specialties and 16 countries (29% being from Saudi Arabia); the majority (88 %) were radiologists. 71% of the respondents reported that they had no knowledge of SBS, and the majority (95%) stated that they did not use SBS in their clinical practice. The respondents indicated that the detailed imaging findings of FD lesion characteristics were used to determine the severity of FD skeletal involvement. Whole-body magnetic resonance imaging followed by bone scintigraphy were the most used imaging modalities when polyostotic FD is suspected.

Conclusion

Despite the dissemination of the international FD/MAS guidelines, 5% of the respondents reported the use of SBS in their clinical practice. We received low response rate; therefore, we proposed possible area of improvement and survey design to increase response rate of a future survey that fits the same aim of this study. This survey emphasised on the implications of wider education and training to increase the awareness of SBS and eventually the use of it in the clinical practice.

5.2 Introduction

Fibrous dysplasia (FD), a rare metabolic bone disease, involves the replacement of normal bone tissue with abnormal fibrous tissue [1-3]. FD can manifest as a single lesion (monostotic FD) or multiple lesions (polyostotic FD), with or without the presence of extra-skeletal manifestations, which is referred to as McCune-Albright syndrome (MAS). The incidence of FD is challenging to assess due to its nature, as some lesions may be asymptomatic and discovered incidentally on diagnostic images. However, FD can also cause severe complications, such as deformities, pathological fractures, progressive scoliosis and functional impairment, leading to the need for ambulatory assistance aids [4].

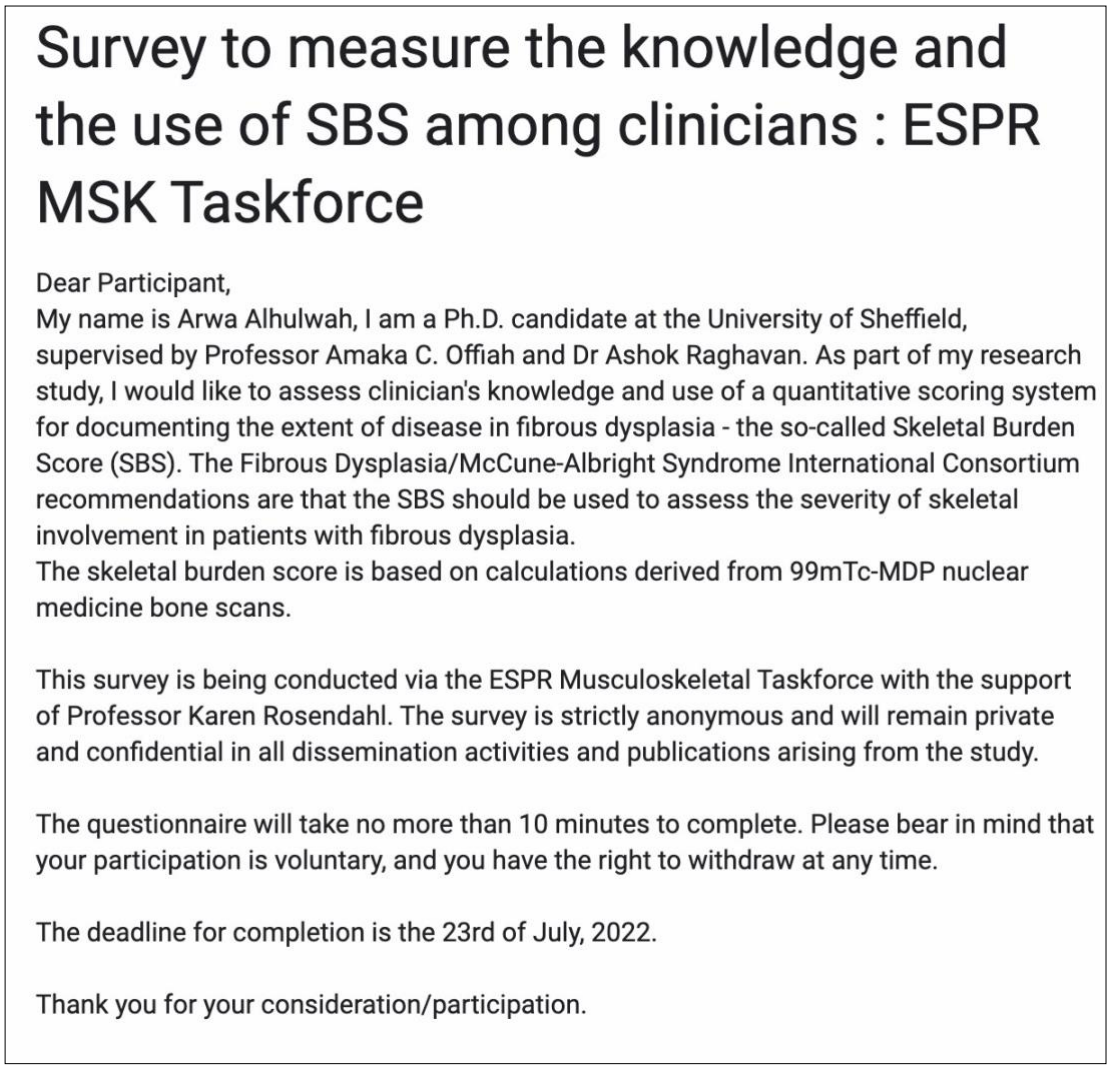
In 2019, a panel of clinical experts from diverse specialties worldwide established guidelines for the diagnosis, treatment, and management of fibrous dysplasia (FD) and McCune-Albright syndrome (MAS) [5]. These guidelines covered FD definition, clinical complications, diagnosis, treatment, surgical procedures, and management. One of the FD/MAS guidelines recommends the use of the skeletal burden score (SBS), a quantitative measure for assessing the skeletal involvement in FD, to evaluate skeletal severity caused by FD/MAS as part of the diagnostic process [6]. Prior studies utilised the SBS as a clinical predictor of disease severity and ambulatory status, and it has demonstrated a high correlation with the quality of life of many patients, making it a dependable assessment tool [6-9]. Although the FD/MAS guidelines recommend using SBS when evaluating FD involvement, its current application in clinical practice has not been investigated. To address this knowledge gap, we developed a short survey to assess the level of knowledge and use of SBS amongst clinicians and the imaging modalities used when suspecting polyostotic FD to document disease burden.

5.3 Methods

5.3.1 Design and setting

This survey was conducted using a web-based platform, Google Forms. A survey link was deployed and sent to the mailing lists of the following societies: the European Society of Paediatric Radiology (ESPR) Musculoskeletal Taskforce, the Saudi Commission for Health Specialties (SCFHS), and the British Paediatric and Adolescents Bone Group (BPABG) on February 28, 2022. The total number of clinicians registered on the societies' mailing lists was around 3,442.

An email reminder with the survey link was sent three to four weeks after the initial invitation. The survey was circulated via email twice during the collection period and was open for responses from February to July 2022. Before commencing the survey, a brief description of the survey's rationale and purpose was provided as well as an estimate of the time it would take participants to complete. Followed by a statement ensuring their anonymity (Figure 5.1).



Survey to measure the knowledge and the use of SBS among clinicians : ESPR MSK Taskforce

Dear Participant,
My name is Arwa Alhulwah, I am a Ph.D. candidate at the University of Sheffield, supervised by Professor Amaka C. Offiah and Dr Ashok Raghavan. As part of my research study, I would like to assess clinician's knowledge and use of a quantitative scoring system for documenting the extent of disease in fibrous dysplasia - the so-called Skeletal Burden Score (SBS). The Fibrous Dysplasia/McCune-Albright Syndrome International Consortium recommendations are that the SBS should be used to assess the severity of skeletal involvement in patients with fibrous dysplasia.
The skeletal burden score is based on calculations derived from 99mTc-MDP nuclear medicine bone scans.

This survey is being conducted via the ESPR Musculoskeletal Taskforce with the support of Professor Karen Rosendahl. The survey is strictly anonymous and will remain private and confidential in all dissemination activities and publications arising from the study.

The questionnaire will take no more than 10 minutes to complete. Please bear in mind that your participation is voluntary, and you have the right to withdraw at any time.

The deadline for completion is the 23rd of July, 2022.

Thank you for your consideration/participation.

Figure 5.1 Survey opening statement

5.4 Measures

The survey questions were designed by the PhD student and her two supervisors, Prof. Amaka C. Offiah and Dr Ashok Raghavan. Additionally, feedback was obtained from a panel of three clinicans, including experts form the UK, with background in radiology to refine the survey prior to its distribution. The survey consisted of 10 questions (Table 5.1), with both open-ended and close ended questions, covering the following parts:

- **Part I:** demographic information, including years in practice, speciality, type of practice, and location.
- **Part II:** close-ended questions to assess the knowledge and use of SBS.
- **Part III:** open-ended questions to investigate the annual number of FD patients seen by respondents in their clinical settings, the methods used for documenting skeletal burden in FD, and preferred imaging modalities.

5.4.1 Statistical analysis

Responses were transferred from Google Forms to a Microsoft Excel spreadsheet for data analysis. Descriptive statistics of the participants' demographics and other characteristics, including absolute counts and percentages, are presented in tables and figures. For the qualitative aspect of the survey, particularly the open-ended questions, a thematic analysis was conducted. In this analysis, responses were explored for underlying themes and categorised accordingly. The findings from this qualitative data are illustrated using visual charts.

Table 5.1 Survey questions

Items	Response Choices
1. **What is your speciality?**	Free text
2. **Years of experience as a consultant.**	□ 0-5 years □ 5-10 years □ 10-15 years □ >15 years
3. **What country do you practice medicine?**	Free text
4.**In what type of hospital do you work? (multiple answers allowed)**	□ General centre □ Adult hospital □ Paediatric hospital □ Teaching hospital
5.**How many FD patients/images do you see or report annually?**	Free text
6. **I have heard about the SBS**	□ Yes □ No □ Unsure
7. **I know how to use the SBS**	□ Yes □ No □ Unsure
8. **I use the SBS when interpreting FD images**	□ Yes □ No □ Unsure
9. **I feel confident using the SBS**	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
10. **If you don't use the SBS, how do you document disease burden in FD?**	Free text

FD, fibrous dysplasia; SBS, skeletal burden score.

5.5 Results

5.5.1 Respondents' characteristics

Table 5.2 summarises the characteristics of the respondents. A total of 59 clinicians from 16 different countries participated in the survey, yielding a response rate of less than 2%. Of these respondents, 29 % were from Saudi Arabia and 27% were from the United Kingdom, with the remaining participants dispersed across various countries. The majority of the participants, accounting for 88 %, were radiologists. About 29 % of the participants were employed in a general setting. In terms of experience, 42 % had over 15 years, 27% had less than five years, 20 % had between five and ten years, and 10 % had between 10 and 15 years of experience.

Table 5.2 Summary of respondent's demographics

Variables	Participants, n (%)
Country of residency Asia	
Saudi Arabia	17 (29)
Europe	
Austria	1 (1.6)
Estonia	1 (1.6)
France	3 (5)
Germany	4 (6.7)
Italy	1 (1.6)
Netherlands	3 (5)
Norway	1 (1.6)
Romania	1 (1.6)
Serbia	1 (1.6)
Slovenia	1 (1.6)
Spain	3 (5)
Switzerland	2 (3.3)
United Kingdom	16 (27)
North America	
United States of America	3 (5)
South America	
Brazil	1 (1.6)
Practice setting	
Paediatrics	27 (46)
Adults	7 (12)
Specialist	20 (34)
Teaching	22 (37)
General	17 (29)
Speciality	
Radiology	52 (88)
Paediatric endocrinology	5 (8.4)
Rheumatology	1 (1.6)
Orthopaedics	1 (1.6)
Years of practice	
0–5 years	16 (27)
5–10 years	12 (20.3)
10–15 years	6 (10)
>15 years	25 (42.3)

5.5.2 Knowledge and use of the skeletal burden score

The bars show three questions which assess the knowledge and use of SBS (Figure 5.2). 71% of clinicians reported they have not heard about the SBS. 86% of the respondents indicated that they do not know how to use the SBS. For the last statement, 86% do not use the SBS when interpreting FD images.

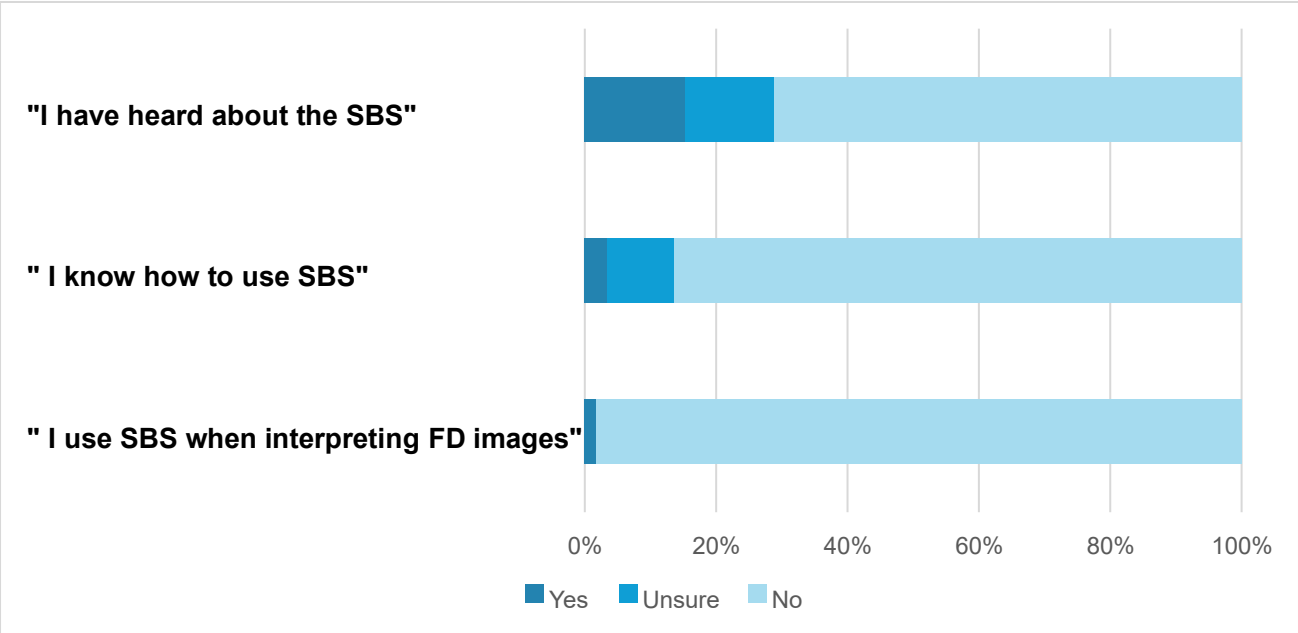


Figure 5.2 Clinicians' awareness and use of the skeletal burden score
FD, fibrous dysplasia; SBS, skeletal burden score

5.5.3 Annual number of fibrous dysplasia patients treated

Responses regarding the annual number of FD patients treated showed significant variation, highlighting disparities in clinician experience with the disease. Most respondents reported managing only one patient per year, which reflects the rarity of the condition. However, one clinician from the United States of America reported seeing an average of 100 patients annually, suggesting a highly specialised practice or centralised referral centre (Figure 5.3).

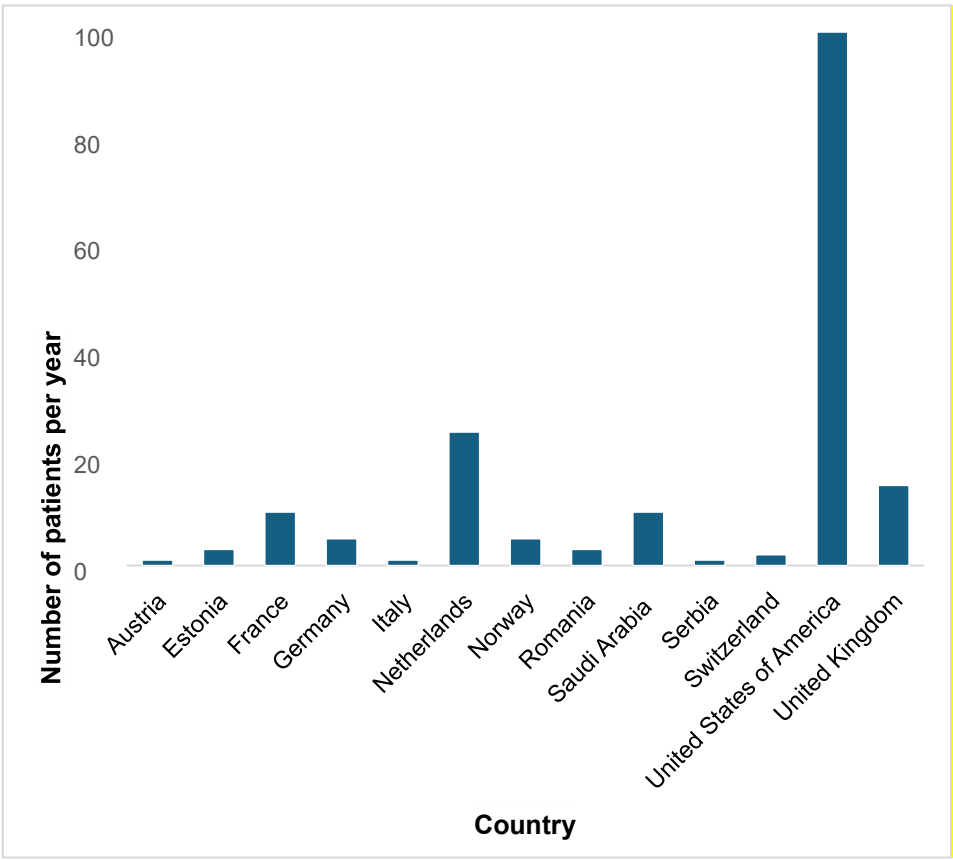


Figure 5.3 The reported number of FD patients per year

5.5.4 Preferred diagnostic modalities

The preferred diagnostic modalities for suspecting polyostotic FD varied among respondents. Whole-body magnetic resonance imaging (WBMRI) was reported as the most utilised imaging modality, followed by nuclear medicine bone scintigraphy. Radiography, regional computed tomography (CT) and MRI scans were also employed, while the EOS™ imaging system was the least utilised (Figure 5.4). These findings highlight a reliance on advanced imaging techniques for detailed anatomical and pathological evaluation in polyostotic FD cases.

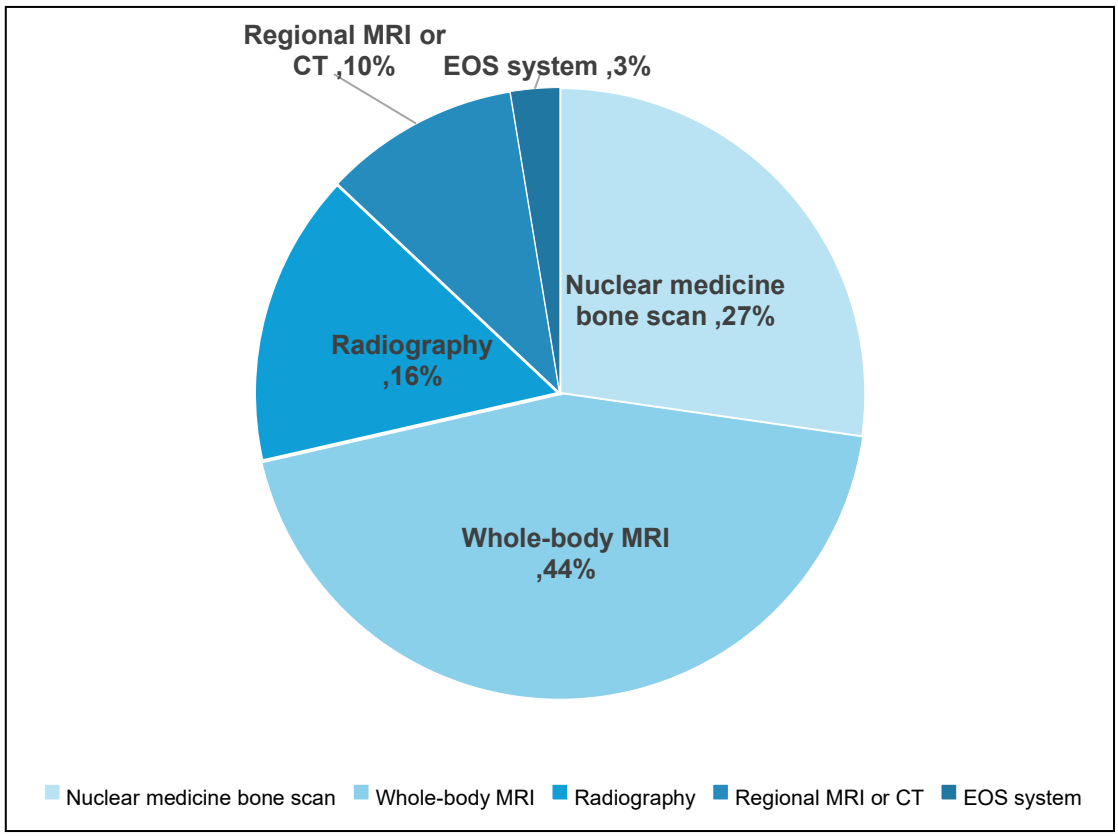


Figure 5.4 The preferred imaging modalities when suspecting polyostotic FD

CT, computed tomography; EOS™ system, Entrepreneurial Operating System®; MRI, magnetic resonance imaging.

5.5.5 Approaches to documenting FD skeletal burden

Respondents reported employing diverse methods to document FD skeletal burden, which could be grouped into four major approaches. The most commonly reported strategy, utilised by 42% of respondents, involved detailed anatomical documentation. This approach described FD lesions based on their number, size, location and avidity, providing comprehensive anatomical characterization crucial for both clinical and research purposes.

Another 17% of respondents highlighted the importance of relying on clinical history and reported symptoms to document FD burden. This included factors such as pain and functional impairment, reflecting a focus on the patient's clinical presentation and the overall impact of the disease on their quality of life. Additionally, eight percent of the respondents mentioned the use of clinical tests, such as bone turnover markers like alkaline phosphatase, as part of their strategy. These biochemical measures offered supplementary insights into disease activity.

Radiological modality-specific approaches were also noted, accounting for 19% of the responses. Among these, conventional radiographs were the most reported (10%), followed by MRI (6%) and bone scintigraphy (3%). These imaging techniques were used to confirm the disease diagnosis and assess skeletal involvement. Overall, the findings reveal considerable variability in how clinicans document FD skeletal burden, underscoring the need for standardised approaches to ensure consistency in practice.

5.6 Discussion

This survey attempted to gather insights into clinicians' knowledge and use of the SBS when diagnosing FD. According to the international FD/MAS guidelines, SBS is recommended for assessing skeletal severity. Therefore, the survey set out to assess clinician’s awareness of SBS and ascertain if the guidelines were being followed.

Most respondents were experienced radiologists, with 42% having over 15 years of experience. However, only nine clinicans were familiar with SBS, and just two confirmed a clear understanding of its application. Importantly, none of the respondents reported using SBS in routine clinical practice. While these findings are limited by the low response rate (less than 3%) and potential response bias-particularly the under-representation of early-career clinicans, they offer valuable insights into possible barriers affecting the use of SBS in clinical practice.

A key barrier appears to be the lack of training. Many clinicans may be unaware of the role of SBS in diagnosing FD/MAS. Training could be delivered in the form of short similar or online module as part of continuing medical education (CME). Another barrier is the complexity of implementing SBS in clinical practice. The score may sound detailed and time-intensive to clinicians. Time constraints is another significant obstacle. Radiologists and other clinicians often face demanding workloads, leaving limited capacity for additional tasks such as applying SBS. Without streamlining or integrating SBS into routine workflows, it may remain underutilised. Finally, the perception of SBS clinical utility could contribute to the low adoption of SBS. Clinicians may not fully appreciate its value in assessing disease severity, particularly in children with FD/MAS. This lack of perceived relevance can lead to hesitation in adopting SBS as a standard part of patient evaluation.

The low adoption rate of SBS in clinical practice, despite its inclusion in the international FD/MAS guidelines, reflects broader challenges in integrating guideline-based tools into routine care. Comparing SBS adoption to other diagnostic tools or scoring systems provides valuable context for understanding these barriers. For example, tools such as the FRAX score for fracture risk faced similar hurdles during early implementation stages [15-16]. These included clinician unfamiliarity, perceived complexity, and limited demonstration of direct clinical benefits. Unlike FRAX, which is supported by significant clinical validation and large-scale adoption campaigns, SBS remains under-recognised, partly due to the rarity of FD/MAS.

Our survey shows that 42% of clinicians assess FD skeletal burden using descriptive details of FD lesions characteristics. The SBS, provides a quantitative representation of FD involvement in eleven compartments of the skeleton, and a total severity score, ranging from 0 to 75, for the entire skeleton. The SBS is the only method for evaluating skeletal burden that is unaffected by bisphosphonate treatment or age [6]. Therefore, many studies used SBS as an indicator of skeletal severity which is more accurate and reliable than ALP. Collins et al [10] demonstrated the predictive powers of SBS in predicting the adult functional outcomes. In a study by Majoor et al [7], found that high SBS associated with impairment of quality of life (QoL).

Respondents favoured WB-MRI as the preferred imaging method for detecting polyostotic FD. The literature reveals that FD lesions display nonspecific traits on MRI scans, which show low to moderate signal intensity on T1-weighted images and high signal intensity on T2-weighted images [11, 12]. The variation in signal intensities and the heterogeneous intensity observed on T2-weighted images are attributable to

variations in the composition of bony trabeculae, collagen, haematological elements, and cystic changes within the FD lesions.

When diagnosing FD, MRI is invaluable for differentiating FD lesions from other cystic-like lesions and malignant tumours, providing detailed anatomical insights into the extent of FD lesions, including aspects such as nerve compression and soft tissue involvement [12, 13]. According to international FD/MAS guidelines, whole-body imaging using WB-MRI, bone scintigraphy, or the EOS system is necessary to accurately diagnose and classify FD in patients older than five years of age [5]. Given the need for more research into the application of SBS alongside WB-MRI, relying solely on WB-MRI may not provide a complete picture of the skeletal burden associated with FD. Thus, the use of bone scintigraphy could be instrumental in aiding clinicians in diagnosing and assessing FD involvement. The development of a formatted Excel spreadsheet embedded with SBS formula or an online SBS calculator, would enhance the accessibility of SBS.

Furthermore, while the survey didn't specifically explore the current state of education or training on SBS, the findings suggest that the low level of SBS usage among clinicians across various specialities may be attributed to a lack of awareness or formal education on its application. Therefore, organising training sessions and developing educational materials such as webinars, and online modules focusing on the application of SBS may encourage and empower clinicians, instilling greater confidence in implementing SBS effectively into clinical practice. Additionally, offering continuing medical education (CME) credits for participation in SBS-focused training may incentivise clinicans to engage in such programmes. Collaboration with international task forces and societies involved in FD research such as European

Society of Paediatric Radiology (ESPR) and other relevant professional bodies, could further facilitate the dissemination and adoption of SBS knowledge in clinical practice.

5.6.1 Limitations & solutions

The extremely low response rate observed in this study represents a significant limitation. Several factors likely contributed to this outcome. One key consideration is the rare nature of FD. The global prevalence of FD is estimated at 1 in every 5,000 to 10,000 individuals, accounting for 2.5% to 5% of all benign bone tumours [1, 3]. Given its low incidence, clinicians may have perceived their participation as less relevant to their routine practice, resulting in hesitancy to engage in the survey.

Another important factor was the timing of the survey dissemination, which coincided with the coronavirus disease 2019 (COVID-19) pandemic lockdowns. During this period, there was a surge in survey-based studies as researchers adapted to global restrictions and sought to continue their work remotely. The pandemic placed immense emotional, social, and economic pressure on clinicians, which likely affected their willingness to participate. Additionally, survey fatigue, a phenomenon where respondents become overwhelmed by frequent survey invitations, may have played a role. This fatigue is often caused by lengthy surveys, complex topics, and an increased number of open-ended questions, all of which can result in incomplete responses or outright termination of participation [14, 15]. One study observed that a rise in survey-based studies accompanied by declining response rates during the pandemic [16]. These factors may have collectively contributed to the low response rate observed in this survey.

A further limitation concerns the geographical distribution of respondents. Notably, 29% of participants were from Saudi Arabia, why may introduce a geographical bias in interpretation of results. This overrepresentation could reflect differences in clinical practice, availability of diagnostic tools, or regional variations in FD management strategies. As a result, the findings may not be entirely generalisable to other regions with different healthcare infrastructures or FD diagnostic protocols. Future studies should aim to achieve a more geographically diverse response pool to ensure broader applicability of findings.

Although the survey targeted all clinicans managing FD patients, the majority of respondents (88%) were radiologists. This likely reflects the pivotal role of radiology in diagnosing FD, as imaging remains a cornerstone of evaluation. However, it also introduces selection bias, with underrepresentation of other specialists such as endocrinologists, orthopaedic surgeons, and paediatricians. As a result, the findings may be more reflective of radiological practice than multidisciplinary clinical management. Future surveys should aim to engage a wider range of specialists to ensure a more representative dataset. In addition to specialty bias, the geographical distribution of respondents was heavily skewed, with clinicans from Saudi Arabia and the United Kingdom accounting for over half of the responses. This geographical concentration limits the applicability of the findings to FD/MAS guidelines in clinical practices, access to diagnostic tools, and guideline implementation may vary significantly between countries. For instance, awareness and utilisation of the SBS may differ in countries with less developed healthcare infrastructure or limited knowledge or access to new scoring system such as SBS in the diagnosis of FD/MAS.

Another limitation of this study is the exclusion use of descriptive statistics, such as percentages and averages, without applying advanced statistical analysis such as chi-square tests and correlation analysis of the variables. Future studies with larger sample size should use inferential statistical methods to enhance the robustness and applicability of the findings.

5.6.2 Future implications and opportunities for improvement

To enhance the relevance and response rate of future survey, one potential approach could involve including an initial screening question: *"Do you see FD patients at your clinics/institutions? "* (yes/no). This question would ensure that only clinicians actively treating FD patients proceed with the survey, while those who do not would conclude their participation at this stage. This approach would refine the respondent pool and provide deeper insights into the reasons for non-responses.

It is important to note that online surveys generally exhibit higher non-response rates compared to other data collection methods, such as face-to-face or telephone interviews [17]. Future surveys could benefit from mixed-method approach, combining online surveys with personalised invitations or follow-up calls to improve. Moreover, this survey did not assess the applicability of the FD/MAS guideline. Including questions to evaluate respondents' knowledge and familiarity with the guidelines would be a valuable addition.

Another potential strategy for improving the generalisability of future survey is to collaborate with international task forces and organisations related to FD/MAS to promote the survey more effectively. Offering incentives, such as professional development credits or endorsement by recognised clinical societies or communities could help increase clinicans engagement and reduce the impact of survey fatigue.

Finally, targeted outreach efforts to engage clinicans from range of multidisciplinary specialties, including endocrinologists, orthopaedic surgeons, and paediatricians, are recommended to ensure more balanced and meaningful findings.

5.7 Conclusion

To the best of our knowledge, this is the first survey to capture clinicians' perspectives following the dissemination of the international FD/MAS guidelines. Although the response rate to the survey was less than 2%, the findings provide preliminary insights into current diagnostic practices for FD on an international scale.

The results emphasise the need for further education and targeted efforts to raise awareness of SBS. While this survey offers a starting point, future studies with improved response rates and more diverse participant representation are essential to validate these findings and draw more generalisable conclusions. Such efforts will help develop a more comprehensive understanding of the global adoption of SBS and its role in managing FD. The data derived from this survey underscore the importance of continuing professional education and guideline dissemination as critical steps toward enhancing the integration of SBS into clinical practice.

5.8 References

1. Chapurlat, R.D. and P. Orcel, *Fibrous dysplasia of bone and McCune-Albright syndrome.* Best Pract Res Clin Rheumatol, 2008. **22**(1): p. 55-69.
2. Collins, M.T.M.D., *Fibrous dysplasia of bone.* Seminars in arthritis and rheumatism, 2012. **42**(5): p. 545545.
3. DiCaprio, M.R. and W.F. Enneking, *Fibrous dysplasia. Pathophysiology, evaluation, and treatment.* J Bone Joint Surg Am, 2005. **87**(8): p. 1848-64.
4. Hartley, I., et al., *Fibrous Dysplasia of Bone and McCune–Albright Syndrome: A Bench to Bedside Review.* Calcif Tissue Int, 2019. **104**(5): p. 517-529.
5. Javaid, M.K., et al., *Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: A consensus statement from the FD/MAS international consortium.* Orphanet Journal of Rare Diseases, 2019. **14**(1).
6. Collins, M.T., et al., *An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone.* J Bone Miner Res, 2005. **20**(2): p. 219-26.
7. Majoor, B.C.J., et al., *Determinants of impaired quality of life in patients with fibrous dysplasia.* Orphanet J Rare Dis, 2017. **12**(1): p. 80.
8. Paul, S.M., et al., *Disease severity and functional factors associated with walking performance in polyostotic fibrous dysplasia.* Bone (New York, N.Y.), 2014. **60**: p. 41-47.
9. Paul, S.M., et al., *PR_117: Walking Speed is Associated With Skeletal Disease Burden Score and Hip Strength and Range of Motion in Persons With Polyostotic Fibrous Dysplasia.* Archives of physical medicine and rehabilitation, 2006. **87**(11): p. e24-e24.
10. Collins, M.T., et al., *An Instrument to Measure Skeletal Burden and Predict Functional Outcome in Fibrous Dysplasia of Bone*.* Journal of Bone and Mineral Research, 2009. **20**(2): p. 219-226.
11. Jee, W.H., et al., *Fibrous dysplasia: MR imaging characteristics with radiopathologic correlation.* AJR Am J Roentgenol, 1996. **167**(6): p. 1523-1527.
12. Utz, J.A., et al., *MR appearance of fibrous dysplasia.* J Comput Assist Tomogr, 1989. **13**(5): p. 845-51.
13. Kushchayeva, Y.S., et al., *Fibrous dysplasia for radiologists: beyond ground glass bone matrix.* Insights into Imaging, 2018. **9**(6): p. 1035-1056.
14. Schini, M., Johansson, H., Harvey, N. C., Lorentzon, M., Kanis, J. A., & McCloskey, E. V. (2024). An overview of the use of the fracture risk assessment tool (FRAX) in osteoporosis. Journal of endocrinological investigation, 47(3), 501–511. https://doi.org/10.1007/s40618-023-02219-9
15. Saeki, C., Saito, M., Kanai, T., Nakano, M., Oikawa, T., Torisu, Y., Saruta, M., & Tsubota, A. (2021). Clinical Usefulness of FRAX Score for Predicting Sarcopenia in Patients with Chronic Liver Disease. Journal of clinical medicine, 10(18), 4080. https://doi.org/10.3390/jcm10184080
16. O'Reilly-Shah, V.N., *Factors influencing healthcare provider respondent fatigue answering a globally administered in-app survey.* PeerJ, 2017. **5**: p. e3785.
17. Lavrakas, P.J., *Encyclopedia of survey research methods*. 2008: Sage publications.
18. de Koning, R., et al., *Survey Fatigue During the COVID-19 Pandemic: An Analysis of Neurosurgery Survey Response Rates.* Front Surg, 2021. **8**: p. 690680.
19. Evans, J.R. and A. Mathur, *The value of online surveys.* Internet Research, 2005. **15**(2): p. 195-219.

Chapter 6:

Evaluation of the Reproducibility Study of the Skeletal Burden Score (SBS) for Fibrous Dysplasia Assessment

6.1 Abstract

Objectives:

To investigate the intra- and inter-reader agreement of five radiologists scoring the from technetium 99m-methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy of patients diagnosed with fibrous dysplasia/McCune-Albright syndrome (FD/MAS) using Skeletal burden score (SBS). Another aim is to compare the reliability of SBS between the Digital Imaging and Communication in Medicine (DICOM) and Joint Photographic Experts Group (JPEG) image formats.

Methods:

A multicentre retrospective assessment was conducted on 26 ^{99m}Tc-MDP bone scintigraphy images from 22 patients diagnosed with FD/MAS. Five radiologists independently scored the bone scintigraphy scans. The intra- and inter-agreement of the SBS were evaluated using intraclass correlation coefficient (ICC) and Bland–Altman plots.

Results:

The intra-reader agreement was excellent, with a mean ICC of 0.98 for both DICOM and JPEG formats (DICOM:0.93-1.00; JPEG: 0.97-0.99). In the BA plot, 7.69% of points were outside the 95% limit of agreement. Inter-reader agreement was also excellent, with a mean ICC of 0.96 (0.92-0.99). In the BA plot, 3.84% of points were outside the 95% limit. The SBS values for JPEG demonstrated reliability equal to DICOM across all five readers.

Conclusion:

Excellent intra-, and inter-reader agreement of SBS among radiologists with diverse subspecialties and experience. The reliability of SBS was consistent across both DICOM and JPEG formats, highlighting its accessibility for clinicians to assess skeletal severity in FD/MAS without prior knowledge or training.

6.2 Introduction

Fibrous dysplasia (FD) is a rare genetic and non-inherited metabolic bone disorder characterised by abnormal fibrous tissue located anywhere within the skeleton [1, 2]. The mosaic nature of FD can range from asymptomatic single monostotic FD lesion to polyostotic FD accompanied by extra-skeletal manifestations, this condition called McCune-Albright syndrome (MAS) [3-5]. In 2019, a panel of experts published international guidelines for FD/MAS. The guidelines highlight the best practice around diagnosis, management and treatment plans to improve the care of FD/MAS patients [6].

One of the recommendations of the international FD/MAS guidelines is staging skeletal involvement of FD/MAS during diagnosis. The staging is by the use skeletal burden score (SBS) [7]. The SBS is a semiquantitative tool that is derived from planar whole-body technetium 99m-methyl diphosphonate (^{99m}Tc-MDP) bone scintigraphy [8]. Many studies have used SBS as a reliable tool to assess skeletal burden instead of relying solely on measuring bone turnover markers such as alkaline phosphatase (ALP). This is because ALP levels are influenced by multiple factors, including sex, ageing, FD subtypes, associated endocrinopathies, and medications such as bisphosphonates [9, 10]. Moreover, ALP levels vary between males and females throughout all life stages. On the other hand, SBS is not affected by changes in age or bisphosphonate treatments [8]. One of the recommendations presented in the guidelines is the importance of surveying the skeleton to assess the skeletal burden using SBS by the age of five [11]. Collins et al. [7] also demonstrated that the SBS had high inter-reader and intra-reader (ICC=0.96 and ICC=0.98, respectively) across six readers with different specialities. Although the specific image format used was not disclosed, the

reliability of SBS suggests that exploring the impact of different image formats could be significant.

In this context, while the digital imaging and communications in medicine (DICOM) format is the standard in radiology departments, the potential of other image formats, such as the joint photographic experts' group (JPEG), has been explored in various studies across different modalities [12-14]. Moreover, DICOM images, while often retaining higher pixel depth (e.g., 12-bit or 16-bit compared to 8-bit in JPEG) and minimal compression are substantial in size, requiring significant storage capacity and specialised software for image review. This higher pixel depth allows for greater grayscale detail, which can enhance the interpretation of subtle skeletal abnormalities. In contrast, JPEG images less pixel depth reducing file size and storage needs but potentially compromising imaging quality and detail. Despite these differences, the resolution of JPEG images may still be sufficient for clinical purposes, offering a practical alternative for clinical use. However, the application of SBS from planar bone scintigraphy using the JPEG image format has not yet been investigated, and its impact on scoring accuracy warrants further study.

The reliability of SBS has not been ascertained outside of the research group that developed it. Therefore, the primary aim of this study was to determine the intra- and inter- reader reliability of SBS derived from ^{99m}Tc-MDP bone scintigraphy scans of FD/MAS patients and compare the findings with those previously reported [7]. The second aim was to assess the reliability of SBS calculated from DICOM, and JPEG image formats.

6.3 Material and methods

6.3.1 Patient cohort

This study is part of a retrospective, multi-centre study of three collaborative sites that included adults and children diagnosed with FD/MAS who had undergone at least one ^{99m}Tc-MDP bone scintigraphy scan between 2006 and 2022 before initiating any treatment or surgical interventions targeting FD lesions. Three collaborating sites: Sheffield Children's Hospital NHS Foundation Trust (SCH), King Faisal Specialist Hospital and Research Centre (KFSHRC), and King Fahad Specialist Hospital (KFSH). The diagnosis of FD/MAS is confirmed by radiological and clinical testing findings. Histopathological testing has been used for use patients to confirm FD/MAS. The collaborated sites perform bone scintigraphy as a gold standard for the diagnosis of FD/MAS or when suspecting polyostotic FD.

6.3.2 Bone scintigraphy

Due to the retrospective nature of the study, specific imaging protocol was not implemented for this study. However, all three sites used a standardised imaging protocol of bone scintigraphy scan. The protocol specifications where; large field of view, low-energy, high-resolution collimator, and a 20% window centred at 140 keV. Images were obtained 3-5 hours after intravenous administration of ^{99m}Tc-MDP. The administrated dose followed the guidelines of the European Association of Nuclear Medicine (EANM), with adult patients receiving a dose ranging between 300-740 MBq (8 – 20 mCi), and paediatric patient receiving a dose range 170-210 MBq (4-6 mCI) with a minimum of 20-40 MBq (0.5-1.0 mCI) [15, 16]. Image acquisition is typically three hours after the intravenous injection of ^{99m}Tc-MDP.

Both anterior and posterior whole-body images were acquired at an imaging speed of 10-15 cm/minute and image resolutions of 64 x 64, 128 x 128, or 256 x 256 pixels. The ^{99m}Tc-MDP bone scintigraphy images were retrieved from the picture archiving and communication system (PACS), from all three collaborated sites in DICOM and JPEG image format. The scanning protocols from SCH and KFSH are provided in Appendix IV. Anonymisation of the images involved the extraction of all patient's identifiable data and each image was given a unique number. To avoid bias, the number of each image was randomly changed for each reading round. For the first reading round, the images were converted from DICOM to JPEG format with an image size of approximately 1110 × 772 pixels and image dots per inch (DPI) of approximately 72 pixels/inch which is the standard for optimal screen resolution. For the second reading round, the same images in JPEG format were used, and randomly given a new number. A washout period of four weeks was implemented between the first and second reading rounds. The third reading round, conducted six months after the second round, involved the use of the original DICOM images. These images were also anonymised by assigning random numbers to ensure unbiased and consistent evaluation across all reading rounds.

6.3.3 Participating radiologists

Five radiologists with varying levels of experience and subspecialties participated as readers in this study. Reader 1 (Prof. Amaka C. Offiah, ACO), and Reader 2 (Ashok Raghavan, AR) are both consultant paediatric radiologists from the United Kingdom with 19 and 16 years of experience, respectively.

Reader 3 (Dr Sarah AlShahwan, SA), Reader 4 (Abdulaziz AlSugair, AS), and Reader 5 (Riyadh Alsalloum, RS) were from Saudi Arabia. Reader 3 is a consultant radiologist with a nuclear medicine fellowship and five years of experience. Reader 4 is a consultant nuclear medicine physician with 25 years of experience, while Reader 5 is a consultant nuclear medicine radiologist with a fellowship in paediatric nuclear medicine and 10 years of experience.

6.3.4 Bone scintigraphy scoring

The skeletal burden score (SBS) is a semi-quantitative tool designed to quantify FD involvement within the skeleton. It is calculated from bone scintigraphy scans and relies on assessing metabolically active FD lesions with high ^{99m}Tc-MDP radiotracer uptake. The SBS formula was presented in **Chapter 2**. In this study, the SBS calculations were done using a formulated SBS Microsoft Excel sheet. All five readers independently assessed the skeletal burden by scoring the ^{99m}Tc-MDP bone scintigraphy images blinded to the patient's clinical history, other than the known diagnosis of FD and to the other readers' scores. The readers in this study were not provided with additional training or specific instructions beyond those outlined in Collins et al.'s paper. This approach was chosen to evaluate how reproducibly the SBS could be applied using the existing methodology without specialised training.

6.3.5 Statistical analysis

The absolute numbers and percentages described discrete demographic and clinical data variables. The continuous variables of the SBS were defined as the median, standard deviation (SD), and interquartile ranges (IQRs). We followed the guidelines for reporting reliability and agreement studies (GRRAS) when reporting the statistical analysis of the continuous variables [17]. The intra- and inter-reader agreement is measured using the intraclass-correlation coefficients (ICC), which is widely used to analyse the intra and inter reliability. We used a two-way random, 95% confidence interval (CI), single measure, and absolute agreement model. The ICCs were interpreted as follows: > 0.9 indicated "excellent," 0.75–0.9 indicated "good," 0.5–0.75 indicated "moderate," and an ICC< 0.5 indicated “poor” agreement [18].

Bland-Altman analysis of the mean estimated difference between readings, or two readers were used as a visual representation of the intra- and inter-reader agreements [19]. Cronbach's alpha (α) was used to measure the internal consistency between the sets of SBS calculated from DICOM and JPEG image formats. The α ranges from 0 to 10, and in the classifications, α ≥ 0.9 indicated "excellent,” 0 indicated "good," "acceptable," “questionable”, and α <0.6 was considered poor internal consistency [20]. All the statistical analyses were performed using IBM SPSS Statistics software for Windows (version 29; IBM Corp., Armonk, USA). BA plots were created using the BA-plotteR web tool [21].

6.4 Results

A total of 26 ^{99m}Tc-MDP scans were obtained from 22 patients (11 males; mean age 28.5 ± 13.4 years). The scans were obtained from patients diagnosed with all three FD subtypes: monostotic FD (n = 11), polyostotic FD (n = 8), and MAS (n = 3). The patients' characteristics are summarised in Table 6.1.

The calculated SBSs for FD subtypes were as follows: patients with monostotic FD had SBSs as low as 0.56 and as high as 11.04; patients with polyostotic FD had SBSs between 1.43 and 29.26; and patients with MAS had SBSs between 3.15 and 17.17. The SBSs provided by all five readers were relatively close to each other (Table 6.2).

Table 6.1 Study cohort characteristics

Study cohort characteristics (n=22)		
Sex		**n patients (%)**
	Female	11 (50)
	Male	11 (50)
Age		
	Year; median ± SD	28.5 ± 13.4
FD subtype		
	Monostotic FD	11 (50)
	Polyostotic FD	9 (40.9)
	McCune–Albright syndrome	2 (9.09)

FD, fibrous dysplasia; SD, standard deviation

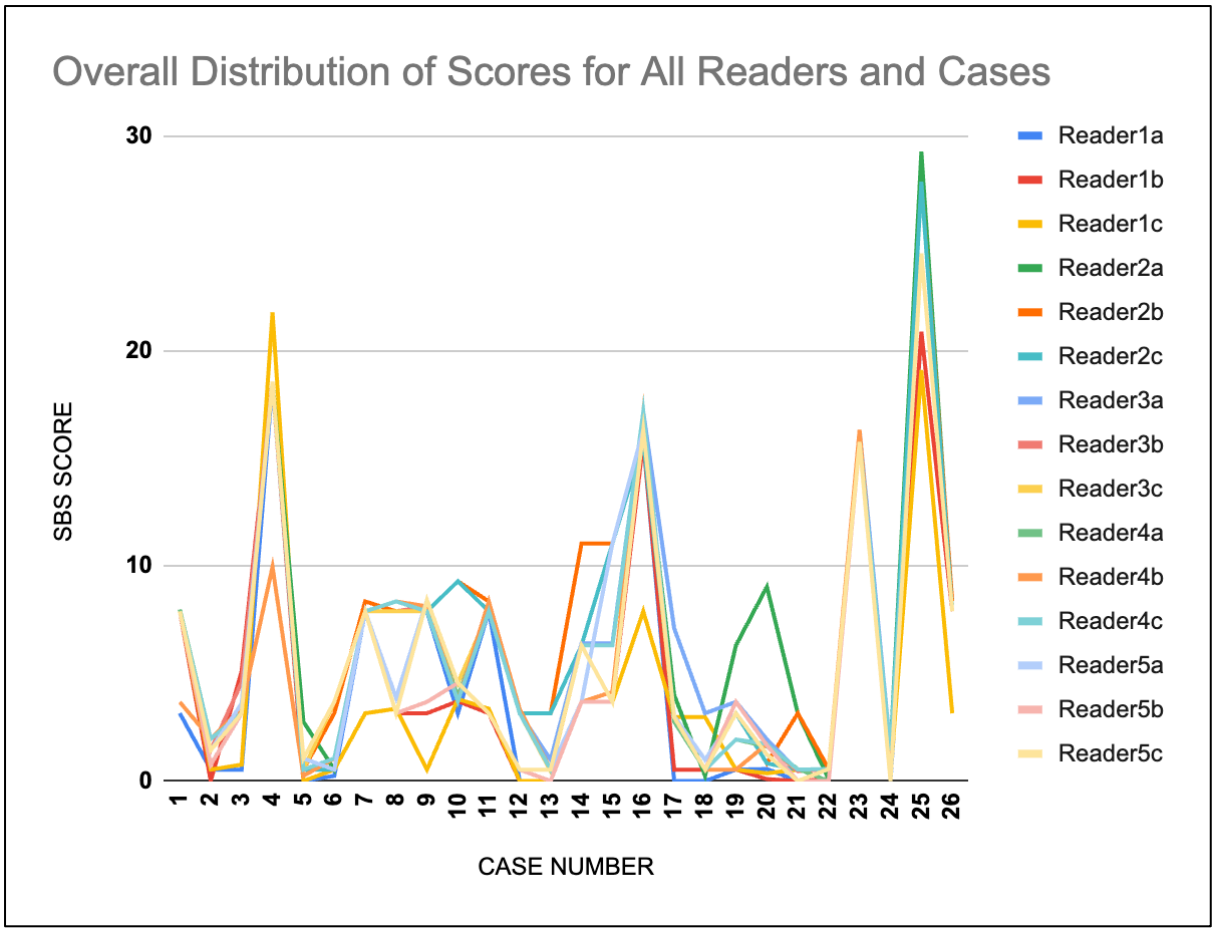


Figure 6.1. Distribution of Scores by Radiologists Across All Cases

Each reader (Reader 1, Reader 2, Reader 3, Reader 4, and Reader 5) scored each case three times. The suffixes **a**, **b**, and **c** represent the first, second, and third set of scores for each reader, respectively. For example, **Reader 1a** refers to the first set of scores by Reader 1, **Reader 1b** to the second set, and **Reader 1c** to the third set of scores.

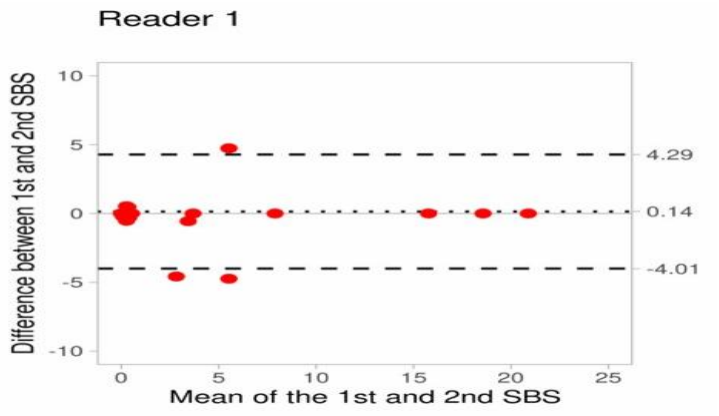
6.4.1 Intra-reader agreement

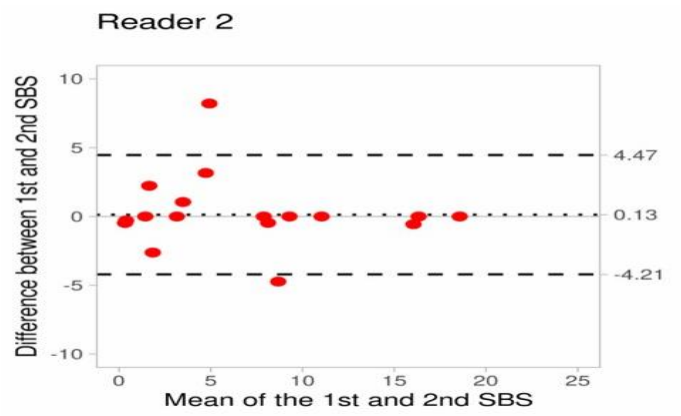
Overall, the intra-reader agreement (agreement between 1st and 2nd reading rounds) for the five readers was excellent with equal to higher than 0.9. When assessing the intra-reader agreement between the 1st and the 3rd reading rounds between JPEG and DICOM image format the intra-reader agreement remains excellent. With slightly higher ICC except for Reader 1 where the ICC of DICOM decreases compared with JPEG. Table 6.2 summarised the other readers' intra-reader agreement.

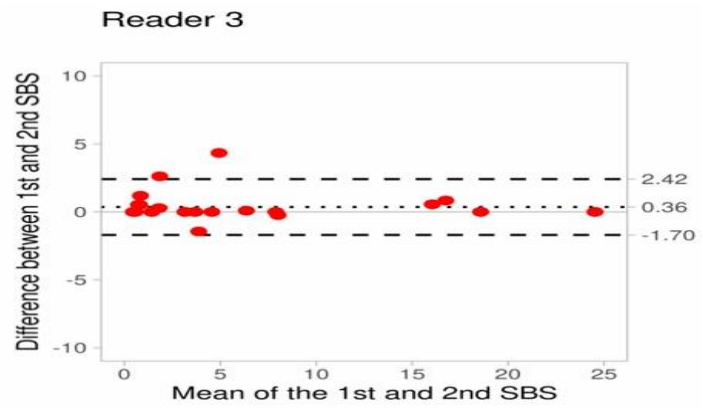
BA analysis of the intra-reader agreement of the 1st and 2nd reading rounds demonstrated a narrow 95% CI and minimal bias for all three scoring rounds. BA plots for the intra-reader agreement for all readers are shown in Figure 6.1.

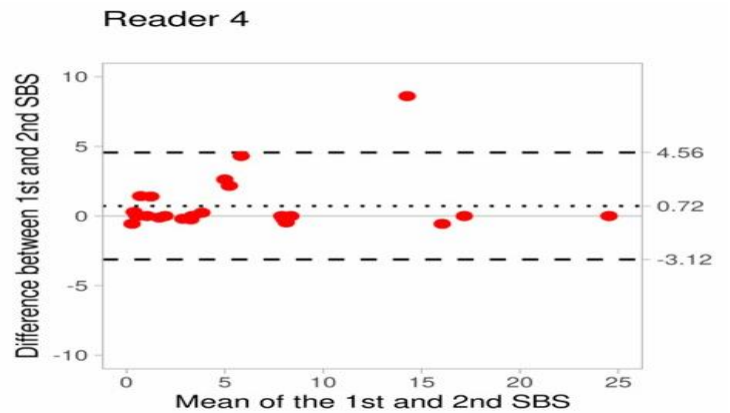
Table 6.2 Intra-class correlation coefficient (ICC) and 95% confidence interval (CI) for intrareader agreement

Reader	1st and 2nd reading		1st and 3rd reading	
	ICC	95% CI	ICC	95% CI
Reader 1	0.970	(0.938, 0.884)	0.930	(0.847,0.969)
Reader 2	0.972	(0.940, 0.988)	0.978	(0.951,0.990)
Reader 3	0.992	(0.982, 0.997)	0.993	(0.984,0.997)
Reader 4	0.972	(0.936,0.988)	1.00	(0.98,1.00)
Reader 5	0.979	(0.954,0.991)	0.983	(0.963,0.992)


Reader 1
Difference between 1st and 2nd SBS
10
5
0
-5
-10
4.29
0.14
-4.01
0
5
10
15
20
25
Mean of the 1st and 2nd SBS


Reader 2
Difference between 1st and 2nd SBS
10
5
0
-5
-10
4.47
0.13
-4.21
0
5
10
15
20
25
Mean of the 1st and 2nd SBS


Reader 3
Difference between 1st and 2nd SBS
10
5
0
-5
-10
2.42
0.36
-1.70
0
5
10
15
20
25
Mean of the 1st and 2nd SBS


Reader 4
Difference between 1st and 2nd SBS
10
5
0
-5
-10
4.56
0.72
-3.12
0
5
10
15
20
25
Mean of the 1st and 2nd SBS

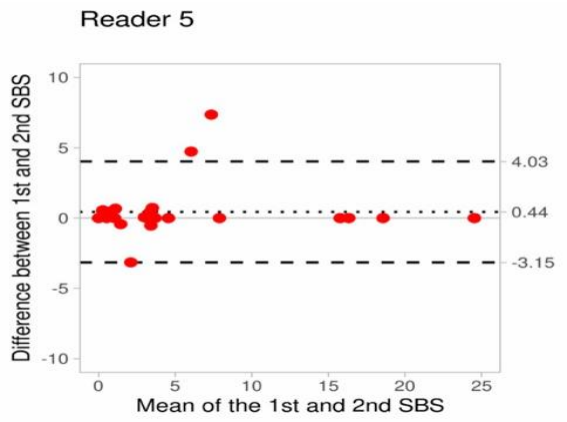


Figure 6. Bland Altman plots of the Intra-reader agreements.
The plots illustrate the agreement between repeated SBS measurements by the same reader. the x-axis represents the mean of the two SBS measurements, while the y-axis represents the difference between the two measurements. the solid line indicates the mean difference (bias), and the dashed lines represent the 95% limits of agreement (mean difference ± 1.96 standard deviations). consistent agreement within the limits suggests good intra-reader reliability.

6.4.2 Inter-reader agreement

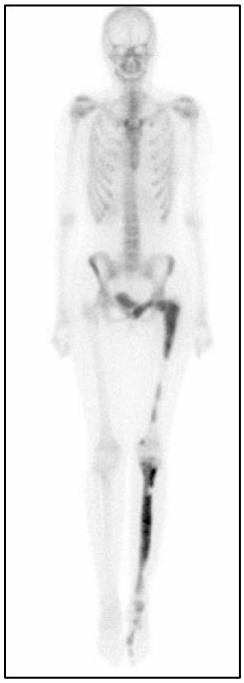
The overall inter-reader agreement ranges from good to excellent, with ICCs ranging from 0.897 to 0.997 for DICOM images and ICCs ranging from 0.921 to 0.991 for JPEG images. The highest agreement was found between Reader 3 and Reader 4, with an ICC of 0.99 (95% CI = 0.97 to 0.99) for both DICOM and JPEG images, while the lowest agreement was found between Reader 1 and Reader 2, with an ICC of 0.90 (95% CI = 0.60 to 0.97) for DICOM and an ICC of 0.92 (95% CI = 0.60 to 0.97) for JPEG. Table 6.3 summarises the inter-reader reliability of all five readers. The BA analysis for the inter-reader agreement demonstrated a broad limit of agreement with a few outliers and a relatively small bias. BA plots of the inter-reader agreements are found in the supplementary file (Appendices IX).

Table 6.3 Inter-reader agreement for skeletal burden score using JPEG image format

Reader pair	JPEG vs JPEG ICC (95% CI)	JPEG vs DICOM ICC (95% CI)
1,2	0.921 (0.602 to 0.974)	0.897 (0.562 to 0.964)
1,3	0.961 (0.682 to 0.988)	0.917 (0.654 to 0.971)
1,4	0.979 (0.842 to 0.994)	0.918 (0.702 to 0.970)
1,5	0.962 (0.911 to 0.983)	0.932 (0.814 to 0.972)
2,3	0.961 (0.914 to 0.982)	0.983 (0.962 to 0.992)
2,4	0.963 (0.901 to 0.985)	0.983 (0.961 to 0.992)
2,5	0.959 (0.851 to 0.985)	0.964 (0.910 to 0.984)
3,4	0.991 (0.977 to 0.996)	0.997 (0.994 to 0.999)
3,5	0.973 (0.932 to 0.989)	0.985 (0.963 to 0.994)
4,5	0.980 (0.955 to 0.991)	0.982 (0.959 to 0.992)

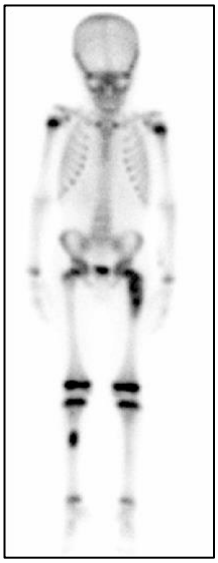
IC, confidence interval; ICC, intraclass correlation coefficient.

a)



Skeletal Compartments	Reader 1	Reader 2	Reader 3	Reader 4	Reader 5
Skull	0	0	0	0	0
Right Upper Extremity	0	0	0	0	0
Left Upper Extremity	0	0	0	0	0
Right Lower Extremity	0	0	0	0	0
Left Lower Extremity	75	75	75	75	75
Spine	0	0	0	0	0
Right Ribs	0	0	0	0	0
Left Ribs	0	0	0	0	0
Sternum	0	0	0	0	0
Right Pelvis	0	0	0	0	0
Left Pelvis	0	0	15	0	0
Total Score	**15.77**	**15.77**	**16.33**	**15.77**	**15.77**

b)



Skeletal Compartments	Reader 1	Reader 2	Reader 3	Reader 4	Reader 5
Skull	0	0	0	0	0
Right Upper Extremity	0	0	0	0	0
Left Upper Extremity	0	0	0	0	0
Right Lower Extremity	2.5	15	15	15	2.5
Left Lower Extremity	15	15	15	15	15
Spine	0	0	0	0	0
Right Ribs	0	0	0	0	0
Left Ribs	0	0	0	0	0
Sternum	0	0	0	0	0
Right Pelvis	0	0	0	0	0
Left Pelvis	0	0	2.5	0	0
Total Score	**3.68**	**6.31**	**6.40**	**6.31**	**3.68**

Figure 6.2 Example of the calculated Skeletal burden scores *Examples of anterior view of bone scintigraphy image (JPEG image formats) and the skeletal burden score from the five readers in JPEG image format. The SBS formula= (0.184 x skull area) + 0.19 x (right upper extremity + left upper extremity)/2 + 0.42x (right lower extremity + left lower extremity)/2 +0.083 x spine + 0.044 x (right rib area + left rib area)/2 + 0.003 x sternum + 0.074 x (right pelvis + left pelvis)/2. SBS score ranges from 0-75.* ***(a)*** *A 23-year-old woman with polyostotic fibrous dysplasia (FD) with perfect inter-reader agreement.* ***(b)*** *A 14-year-old boy with monostotic FD with moderate inter-reader agreement.*

6.5 Discussion

Compliance with the international FD/MAS guidelines, which recommend using the SBS to assess FD involvement which is an indication of disease severity. To the best of our knowledge, this study is the first to validate reader agreement beyond the team that developed the SBS [7]. The findings of this study corroborate those of a previous study conducted by Collins et al. [7]. Our analysis demonstrated an excellent intra- and inter-reader agreement, with a mean ICC of 0.97, which is consistent with the ICC reported by Collins et al. [7]. Moreover, the reliability of the SBS measured using JPEG images was comparable to that of DICOM image format.

The panel of readers consisted of radiologists from various subspecialties with differing years of experience. It was noted that the radiologists with less experience (e.g., Reader 3) tended to assign higher SBS compared to their more experienced counterparts (≥10 years) in terms of speciality. Also, we found that SBS assigned by the nuclear medicine radiologists (Readers 3, 4, and 5) were more similar to each other than those of diagnostic radiologists (Readers 1 and 2). This observation may be attributed to the nuclear medicine radiologists' expertise in interpreting bone scintigraphy images. However, due to the lack of a definitive SBS reference standard, it remains unclear whether the nuclear medicine radiologists consistently overscored or if the diagnostic radiologists consistently underscored the images. Despite the variation in SBS among readers, for example, Reader 1 consistently underscoring, the internal consistency was deemed to be excellent. The internal consistency measures were recorded as follows: Reader 1 ($\alpha = 0.96$), Reader 2 ($\alpha = 0.98$), Reader 3 ($\alpha = 0.99$), Reader 4 ($\alpha = 0.98$), and Reader 5 ($\alpha = 0.99$).

Our analysis revealed that cases presenting with limited FD lesion spread (SBS < 7) demonstrated lower agreement among readers, whereas cases with extensive FD involvement (SBS ≥ 7) exhibited greater consensus. This difference can be attributed to two main factors; first, extensive FD involvement is easier to identify and objectively quantify, whereas FD lesions with mild involvement can be missed or more challenging to score. Which may result in greater variability among readers. In contrast, extensive FD involvement is more visually prominent and easier to identify and quantify objectively.

Second factor is that planar bone scintigraphy images depict overlapping anatomical regions, such as the thorax, spine, and pelvis. This overlap may introduce uncertainty and reduce reader agreement, particularly in cases with minimal skeletal involvement.

Despite the observed disparity in reader agreement for low SBS scores, the differences were minimal and did not necessitate any changes in the management or care of FD/MAS patients. In our cohort, SBS values ranged from 0.56 to 29.2, which fall within the range considered as mild to moderate skeletal burden. According to the literature, an SBS score exceeding 30 in FD/MAS children is associated with functional impairment, whereas scores below 30 indicate mild skeletal severity and are not predictive of long-term functional outcomes [6, 22].

Anatomical compartments with overlapping regions, such as the pelvis and femur, are the most reader disagreements occur. Figure 6.2, highlights variability in SBS assessments among readers, particularly in the pelvis compartments. In Figure 6.2a, Reader 3 assigned a score of 15 to the left pelvis, while all other readers scored this compartment as 0 (indicating no involvement). This discrepancy resulted in a total SBS score of 16.33 for Reader 3 compared to 15.77 for the other readers.

The femur, one of the most common sites for FD lesions, is classified within the lower extremities in the SBS, which account for 42% of the skeleton. In Figure 6.2b, the patient exhibited polyostotic FD with bilaterally in both the right and the left femur, as well as the right lower extremity. Importantly, ^{99m}Tc-MDP normal uptake was observed in growth plates, a common feature in paediatric and adolescent patients undergoing bone development. Reader 3 was the only reader to report involvement of the left pelvis, with a score of 2.5. This discrepancy highlights potential confusion in distinguishing between FD involvement in pelvis and lower extremities compartments.

Such variability underscores the need for improved reader training. Future training could focus on clarifying areas of anatomical overlapping and providing examples of common challenges in assessing SBS, to enhance readers confident and reduce SBS inconsistencies between multiple readers.

The focus of this study on planar bone scintigraphy is based on the original methodology established by Collins et al. (2015), which introduced the SBS using bone scintigraphy. This approach was chosen to ensure consistency with the original study and to evaluate the reproducibility of SBS across different readers. While other imaging modalities such as computed tomography (CT), and magnetic resonance imaging (MRI) are widely used in the diagnosis and evaluation of FD due to their superior anatomical details, they are not currently utilised for SBS scoring. Moreover, single-photon emission computed tomography combined with low-dose computed tomography (SPECT/CT) provides three-dimensional whole-body images with enhanced anatomical details from CT, potentially improving image resolution. Future research should explore the reliability of SBS using SPECT/CT bone scan and compare the results with the findings of this study. Another

potential area for future research is the application of automated software, particularly artificial intelligence (AI), to delineate affected areas and automatically calculate the SBS. AI-based imaging technologies, particularly deep learning methods, have demonstrated substantial promise in medical imaging for tasks such as lesion detection, segmentation, and automated scoring across various conditions. Automated segmentation algorithms could precisely identify FD lesions on planar bone scintigraphy, reducing inter-reader variability and improving the consistency of SBS scoring. However, it is important to note that AI models require large, annotated datasets to achieve robust performance. Given the rarity of FD/MAS, assembling sufficient high-quality imaging data for AI training and validation poses a significant challenge. Collaborative multi-centre efforts and centralised imaging databases would be essential to overcome this limitation and realize the full potential of AI-based automated scoring for FD.

6.5.1 Limitations

One of the primary limitations of this study is the small sample size. While this relatively small cohort limits the statistical power and affects the overall ability to draw definitive conclusions regarding SBS reliability, it reflects the inherent challenges of studying rare diseases such as FD. The rarity of the condition studied, combined with the time constraints of the research period, posed significant barriers to recruiting a larger cohort. Second limitation is the absence of a definitive reference standard for SBS scoring. While the readers relied on the SBS formula described by Collins et al [7], it is difficult to determine whether readers are consistently overscoring or underscoring the involvement of FD. This ambiguity could lead to variability in the interpretation of skeletal burden, potentially influencing the uniformity of findings across different studies and readers. The absence of clinical correlation in this study is another important limitation. Without linking SBS scores to clinical outcomes, it is unclear how variations in scoring impact clinical decision-making, such as monitoring disease progression, assessing treatment response, or surgical interventions.

However, the SBS has potential clinical utility. It provides a standardised, quantitative method for assessing skeletal involvement in FD, which could be valuable for longitudinal patient diagnosis and monitoring disease progression. Also, small differences in SBS scores may influence treatment decisions in patients with borderline or progressive disease, particularly where disease burden is significant, or symptoms warrant closer evaluation. Future studies incorporating clinical outcomes will be essential to validate the SBS as a reliable tool for guiding therapeutic decisions and improving patient management.

Third limitation, the number of patients with moderate to severe FD (SBS > 30) was lower compared to those with mild to moderate FD (SBS < 30). Although there was greater agreement among cases with severe disease, the overall observer agreement remained excellent.

Lastly, the study sample was derived from three collaborating medical centres—two in Saudi Arabia and one in the United Kingdom. While this multi-centre approach enhances the robustness of the findings, it remains geographically limited and may restrict the generalisability of the results to broader, more diverse patient populations. Additionally, the cohort consisted of FD/MAS patients who underwent scintigraphy scans between 2006 and 2022. Although this timeframe ensured the inclusion of relevant cases, the study does not claim to represent the full clinical spectrum of FD/MAS patient population. Despite these limitations, the findings provide valuable preliminary insights into the reliability of the SBS for assessing skeletal severity. Future research with larger cohorts, building on the multi-centre design of this study, is necessary to further validate these findings and enhance their applicability among radiologists with diverse specialities and experience levels.

6.6 Conclusion

We concluded that the present findings confirm high intra- and inter-reader agreement for the SBS among radiologists with diverse subspecialties and experience levels, even without prior knowledge or training. The high reliability of the SBS was maintained across both DICOM and JPEG image formats, underscoring its accessibility and eliminating the need for specialised training in SBS calculations.

By acknowledging the limitations, the study remains transparent about its score while emphasising its importance as a stepping stone for future studies in assessing reliability of SBS using other imaging modalities and across larger study populations.

6.7 References

1. Hartley, I., M. Zhadina, M.T. Collins, and A.M. Boyce, *Fibrous Dysplasia of Bone and McCune-Albright Syndrome: A Bench to Bedside Review.* Calcif Tissue Int, 2019. 104(5): p. 517-529.
2. Feller, L., et al., *The nature of fibrous dysplasia.* Head Face Med, 2009. 5: p. 22.
3. Kushchayeva, Y.S., et al., *Fibrous dysplasia for radiologists: beyond ground glass bone matrix.* Insights Imaging, 2018. 9(6): p. 1035-1056.
4. Dumitrescu, C.E. and M.T. Collins, *McCune-Albright syndrome.* Orphanet J Rare Dis, 2008. 3: p. 12.
5. Spencer, T., K.S. Pan, M.T. Collins, and A.M. Boyce, *The Clinical Spectrum of McCune-Albright Syndrome and Its Management.* Horm Res Paediatr, 2019. 92(6): p. 347-356.
6. Majoor, B.C.J., et al., *Determinants of impaired quality of life in patients with fibrous dysplasia.* Orphanet J Rare Dis, 2017. 12(1): p. 80.
7. Collins, M.T., et al., *An Instrument to Measure Skeletal Burden and Predict Functional Outcome in Fibrous Dysplasia of Bone.* Journal of bone and mineral research, 2005. 20(2): p. 219-226.
8. Collins, M.T., et al., *An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone.* J Bone Miner Res, 2005. 20(2): p. 219-26.
9. Wang, J., et al., *Increasing serum alkaline phosphatase is associated with bone deformity progression for patients with polyostotic fibrous dysplasia.* J Orthop Surg Res, 2020. 15(1): p. 583.
10. Florenzano, P., et al., *Age-Related Changes and Effects of Bisphosphonates on Bone Turnover and Disease Progression in Fibrous Dysplasia of Bone.* Journal of Bone and Mineral Research, 2019. 34(4): p. 653-660.
11. Javaid, M.K., et al., *Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium.* Orphanet J Rare Dis, 2019. 14(1): p. 139.
12. Awang, N., et al. *Digital Planning of High Tibial Osteotomy Using Dicom versus Jpeg formats*. in *2022 International Visualization, Informatics and Technology Conference (IVIT)*. 2022.
13. Saez, D.M., S. Bommarito, and E.K. Sannomiya, *Reproducibility of cephalometric landmarks on posteroanterior digital radiographs using DICOM and JPEG formats.* Oral Radiology, 2016. 32(2): p. 79-86.
14. Trieu, P.D., M. Barron, and S.J. Lewis, *Use of Full-quality DICOM Images Compared to Minimally Compressed Mammograms in JPEG Format for Radiology Training: A Study From Radiologist and Radiographer Perspectives.* Academic Radiology, 2023. 30(8): p. 1748-1755.
15. Van den Wyngaert, T., et al., *The EANM practice guidelines for bone scintigraphy.* Eur J Nucl Med Mol Imaging, 2016. 43(9): p. 1723-38.
16. Bartel, T.B., et al., *SNMMI procedure standard for bone scintigraphy 4.0.* Journal of nuclear medicine technology, 2018. 46(4): p. 398-404.
17. Kottner, J., et al., *Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed.* J Clin Epidemiol, 2011. 64(1): p. 96-106.
18. *"Forming inferences about some intraclass correlations coefficients": Correction*. 1996, American Psychological Association: US. p. 390-390.
19. Bland, J.M. and D.G. Altman, *Measuring agreement in method comparison studies.* Statistical Methods in Medical Research, 1999. 8(2): p. 135-160.
20. Tavakol, M. and R. Dennick, *Making sense of Cronbach's alpha.* Int J Med Educ, 2011. 2: p. 53-55.
21. Goedhart, J. and M. Rishniw, *BA-plotteR - A web tool for generating BlandAltman plots and constructing limits of agreement.* Res Vet Sci, 2021. 137: p. 281-286.
22. Kelly, M.H., et al., *Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone.* Bone, 2005. 37(3): p. 388-94.
23. Javaid, M., et al., *The RUDY study platform–a novel approach to patient driven research in rare musculoskeletal diseases.* Orphanet journal of rare diseases, 2016. 11: p. 1-9.

Chapter 7:

The Assessment of the Quality of Life and the Skeletal Burden in Fibrous Dysplasia Patients from Saudi Arabia

7.1 Abstract

Aims

This study aimed to measure the quality of life (QoL) and bone pain in patients diagnosed with fibrous dysplasia/McCune-Albright syndrome (FD/MAS) in Saudi Arabia. And to assess factors influencing the QoL of our patient cohort.

Methods

This cross-sectional study was conducted on patients treated at King Faisal Specialist Hospital and Research Centre (KFSHRC) and King Fahad Specialist Hospital (KFSH) in Saudi Arabia. The 36-item Short Form Health Survey (SF-36) and Brief Pain Inventory (BPI) questionnaires were used to assess QoL and pain at baseline and six-month follow-up. The measurement of skeletal burden score (SBS) of total compartments SBS_{total} and $SBS_{(legs + pelvis)}$ derived from bone scintigraphy scans. Relationship between outcome measures, SBS and patient demographic data were assessed. Regression analysis was conducted to measure the predictive power of SBS with SF-36 physical domains.

Results

A total of 21 individuals participated in this study, with 52.4% female, a mean age of 33.6 years, and 52.4% monostotic FD. Females reported a lower QoL and three times greater pain intensity than males. Patients with severe FD involvement reported greater pain intensity and interference than those with monostotic FD. $SBS_{(legs + pelvis)}$ demonstrated a strong relationship ($r = -0.5$, $p = 0.02$) with the role-limited due to physical health (RP) SF-36 domain in males. Weak correlations found between SBS and other variables in female patients.

Conclusion

Our study showed that Saudi female patients with FD/MAS reported greater pain and poor QoL compared to male counterparts. The measured $SBS_{(legs + pelvis)}$ was predictor of RP domain of SF-36 in male patients of our cohort. The QoL of patients with FD/MAS in Saudi Arabia require further investigation to understand impact of the disease and the difference between sexes.

7.2 Introduction

Fibrous dysplasia (FD) is a rare metabolic bone disorder that accounts for 2.5% of all bone tumours and is characterised by the replacement of normal bone with abnormal fibrous tissue [1, 2]. The FD incidence rate is about 1 in 10,000 [3]. FD Lesions can be single (monostotic FD) or multiple (polyostotic FD) [4]. McCune-Albright syndrome (MAS) is a severe form of FD that is accompanied by extra-skeletal manifestations, such as café-au-lait and endocrinopathies. FD can cause a wide range of clinical complications, which include bone pain, pathological fractures, scoliosis, bone deformity, and severe physical disabilities. Not all FD lesions are symptomatic; some are asymptomatic and discovered incidentally through medical imaging of unrelated abnormalities [1, 2].

In 2019, the first international FD/MAS consortium of clinical experts published detailed best practice guidelines that defined FD and its clinical complications. The guidelines also provided methods to diagnose, treat, and manage FD/MAS [5]. One of the FD/MAS recommendations is the use of the skeletal burden score (SBS) to quantify the FD involvement determined by a planar nuclear medicine bone scintigraphy scan. The SBS was correlated with the physical component of 36-item short form (SF-36) quality of life (QoL) questionnaire, and it was found that a SBS of more than 30 predicts functional impairment [6, 7]. Another International FD/MAS consortium recommended the use of patient-reported questionnaires to assess the QoL, bone pain and other outcome measures. Furthermore, such instruments allow patients to report their perceptions, health status and coping mechanisms [8] , as well as the impact of FD/MAS on the patient’s physical and mental health [7, 9, 10].

The assessment of the QoL in patients with FD/MAS across the full spectrum of FD has attracted considerable research interest in recent years. A study conducted at the National Institutes of Health (NIH) found that both paediatric and adult patients with FD/MAS experience significant impairments in physical functioning, with female showing greater emotional and mental health challenges compared to male participants [7] Similarly, a study of Dutch FD/MAS patients highlighted similar impairments in physical functioning, further demonstrating the burden of the disease across different population [9]. Research has also focused on the prevalence of pain in FD/MAS [11]. demonstrated that adult FD/MAS patients experience greater pain, particularly in the lower extremities, than paediatric patients, which may be due to cumulative skeletal burden and disease progression over time.

In Saudi Arabia, research on FD/MAS remains limited, particularly the assessment of QoL and pain outcomes. This study aims to address this gap by (1) evaluating QoL and pain-measured using the SF-36 and the brief pain inventory (BPI) in Saudi patients with FD/MAS, and (2) correlating SBS with outcome measures and indicators of disease severity, including alkaline phosphatase (ALP), FD subtype, and ambulatory status. We hypothesised that the lower extremity components of the SBS would have a stronger correlation with physical outcome measures than the total SBS.

7.3 Materials and methods

Patients were recruited from two tertiary care centres in Saudi Arabia: King Faisal Specialist Hospital and Research Centre (KFSHRC) in Riyadh, and King Fahd Specialist Hospital (KFSH) in Dammam. We searched the hospital electronic systems for patients with confirmed cases of FD/MAS.

Patients lists from both centres were reviewed against the following inclusion criteria: (1) patients with a confirmed diagnosis of FD/MAS through medical imaging, clinical assessment and/or histopathological confirmation (if available), (2) the patient had a bone scintigraphy scans done between 2007 and 2022, and (3) the patient did not receive bisphosphonate or denosumab treatment while participating during this study, because, the use of these treatments may affect the intensity of bone pain and its interference with daily activities caused by FD/MAS. Eligible patients were introduced to the study and given information sheets, and any questions were addressed before obtaining written consent from adults and assent from children and their parents.

7.3.1 Ethics approval

We obtained ethical approval to conduct the study from IRAS (ID # 277033) with REC reference (21/EM/0094, July 2021) in the UK followed by institutional review and approval from KFSHRC (RAC # 2211203, December 2021), and KFSH (ORTH 0001, October 2021). All participants were given patient information sheets and signed written consent forms (all in Arabic) before participating in the study.

7.4 Measures

7.4.1 Skeletal burden score

The SBS is a quantitative scoring tool calculated from 99m-technetium-methyl diphosphonate (^{99m}Tc-MDP) bone scintigraphy scan. SBS is a validated tool that assess the skeletal severity caused by FD/MAS involvement. The fundamentals and the SBS formula were previously presented in **Chapter 2**.

For this study we used two SBS scores; the total SBS labelled as SBS_{total}, and the SBS of the (right leg + left leg+ right pelvis + left pelvis) segments and named $SBS_{(legs + pelvis)}$. Bone scintigraphy images were anonymised and imported as JPEG images for scoring purposes. The images were scored by two radiologists (Prof. Amaka Offiah, ACO, and Dr Ashok Raghavan, AS), who were unaware of the patient's medical history. The average SBS calculated by the two radiologists was used in this study. The SBS calculations were carried out using a formulated Excel sheet, provided by Dr. Michael Collins.

7.4.2 Clinical and demographic variables

Demographic and clinical data including sex, age, age at diagnosis, FD subtype, ambulatory status, history of bisphosphonate, surgical procedures, presence of scoliosis, and measured ALP near the date of the bone scintigraphy were extracted from the patient medical records.

The patients self-reported their ambulatory status, which was categorised into three groups: independent ambulation, crutches/canes, and wheelchair. For ALP, the normal ranges are females age between 16-19 years (50–130U/L) and (50–135 U/L) for >19 years. For males the ALP normal range (65-260 U/L) for 16-19 years, and (45-125 U/L) for >19 years [12].

7.4.3 SF-36 questionnaire

The SF-36 is the most used QoL questionnaire in studies on FD and is recommended by the international FD/MAS guidelines. The reliability of the Arabic version of the SF-36 has been shown to exceed 70% among the Saudi population [13], which aligns with the acceptable thresholds in psychometric studies. However, this reliability level is on the lower end when compared to SF-36 results reported in other middle eastern populations, such as in Lebanon, where Cronbach's alpha exceeded 0.798 [14].

The SF-36 contains 36 items that covers eight domains: physical functioning (PF), which consists of 10 items; role limitations due to physical health (RP) with 4 items; role limitations due to emotional problems (RE) with 3 items; vitality (VT) with 4 items; mental health (MH) with 5 items; social functioning (SF) with 2 items; bodily pain (BP) with 2

items; and general health (GH) with 5 items. The score for each question ranges from 0 to 100, and a higher score indicates a better health status [15].

The SF-36 domains are designed to measure an independent aspect of health; however, the domains are related to each other as physical, emotional and social health are often influence each other in real-world.

7.4.4 Bone pain inventory

The BPI is a short, validated, and self-administered assessment tool used to measure pain intensity and pain interference. The World Health Organisation (WHO) developed the BPI in collaboration for symptom evaluation in cancer care, primarily to assess pain in cancer patients. It has been used to assess both chronic and acute pains associated with various diseases [16]. The BPI consisted of 16 items, which are divided into three sections: pain location, pain severity, and pain interference with daily activities. The pain location section enabled the participants to pinpoint the exact location of their pain on a human figure. Pain severity is used to measure worst pain, average pain, least pain, and current pain. The average pain intensity is the sum of all four dimensions. The pain intensity score range is classified as follows: (1-4) mild pain, (5-8) moderate pain, and (9–10) severe pain. The second part of BPI is pain interference, which measures the impact of pain on the following dimensions: mood, sleep, general activity, walking ability, enjoyment of life, relations with other people, and normal work. The average of pain interference is the sum of the seven pain interference dimensions. The pain severity and interference scores range from 0 (no pain or interference) to 10 (severe pain or complete interference) [17]. BPI in Arabic demonstrated excellent reliability, and high cultural

sensitivity among the Lebanese population [12]. BPI and SF-36 were administered twice during this study, once at baseline and again at six-month follow-up. The six-month mark was chosen as the endpoint to evaluate the short-term outcomes and assess changes of QoL of the patient cohort.

7.4.5 Statistical analysis

Continuous variables: age, age at diagnosis, SF-36 subscales, BPI dimensions, SBS_{total}, $SBS_{(legs+\ pelvis)}$ and ALP level were presented by the mean and standard deviation (mean ± SD). Categorical variables: FD subtype, sex, ambulatory status, history of fractures, presence of scoliosis, and treatment history were presented as frequencies and percentages (n, %). Changes between the baseline and six months follow-up were measured by the mean difference, the 95% confidence interval (CI), the p-value, and analysed by independent t-test. Box-whisker plots which were used as a visual (descriptive) representation of the changes of the SF-36 and BPI during baseline and follow-up. Ceiling and floor effects were inspected by eyeball. For correlation analysis between SBS with other clinical variables. we used Pearson correlations (*r*), the interpretation as follows; r=1.0 perfect correlation, r=0.8-0.99 strong, r=0.5-0.79 moderate, r=0.2-0.49, weak and r=0-0.19 no association [18, 19]. The sign of correlation whether positive or negative measures the direction of correlation. P-values less than 0.05 were considered as statistically significant.

7.4.6 Regression analysis

To predict the dependent variables, we performed linear regression analysis on physical function SF-36 domains with strong Pearson correlations only. An important element of regression analysis is the measurement of how the statistical models are able to predict an outcome and evaluate the strength of the relationship between independent and dependent variables. This is expressed by coefficient of determination (r^2), which ranges from 0 to 1. The closer r^2 is to 1 the better the explained variation by the independent variable and the dependent one. In reality, r^2 is never equal to 1, this might be due to the presence of random noise [20]. Significance level (α) was set at 0.05. These relationships are shown as scatter plots and the regression line. All statistical analyses were performed using STATA version 17 software (Stata Corp. LP, College Station, TX, USA) and IBM SPSS statistics version 29 (IBM Corp., Armonk, N.Y, USA).

7.5 Results

The PACs search yielded to 69 patients from both collaborating sites. After applying the inclusion criteria only 28 patients were recruited of which seven patients refused to participate. Twenty-one patients consented and returned the completed QoL and BPI questionnaires at baseline and follow-up phases.

7.5.1 Patient characteristics

The demographic data are summarised in Table 7.1. the majority were female FD/MAS patients. The mean age of the patient cohort was 33.67 years ± 11.39 with a range between (18 - 66) years. Age at diagnosis was 19.62 years ± 10.84 with a range between (4 - 40 years). 52.3% were diagnosed with monostotic FD, 57.1% and patients had no surgical corrections to the FD lesions, and 76.1% patients reported no history of fractures in the FD lesion area. 71.4% were immobilised independently.

The mean of SBS_{total} was 9.41 ± 9.76 with a range between (0.45 – 31.54). The mean SBS_{total} in females was 6.9 and 12.13 in males. The mean of the $SBS_{(legs + pelvis)}$ was 5.78 ± 8.60 with a range between (0- 29.26). The mean $SBS_{(legs + pelvis)}$ was 4.0 in females, and 7.74 in males. Not all patients had their ALP measured around the time of ^{99m}Tc-MDP bone scan. The reported ALP for female participants, ranged between (35-131 U/L) and (49-198 U/L) in male participants.

Table 7.1 Descriptive characteristics of the patient cohort

Variable		mean (SD) or n, (%)
Age (years)		33.67 ± 11.39
Age at diagnosis (years)		19.62 ± 10.84
Sex	*Female*	11 (52.4)
	Male	10 (47.6)
FD subtype	*MFD*	11 (52.4)
	PFD	9 (42.9)
	MAS	1 (4.8)
Ambulatory status	*Independent*	15 (71.4)
	Crutches/ canes	5 (23.8)
	Wheelchair	1 (4.8)
Fracture history	*Yes*	5 (23.8)
	No	16 (76.2)
Surgical history	*Yes*	9 (42.9)
	No	12 (57.1)
SBS $_{\text{(legs + pelvis)}}$		5.78 ± 8.60
SBS $_{\text{total}}$		6.43 ± 7.37
ALP levels (IU/L)	*Total*	80.65 ± 38.36
	Female	71.25 ±30.21
	Male	95.42 ± 47.24

Abbreviations; ALP, alkaline phosphatase; MAS, McCune-Albright syndrome; MFD, monostotic fibrous dysplasia; PFD, polyostotic fibrous dysplasia; SBS, skeletal burden score; SD, standard deviation.

7.5.2 Measured quality of life

Table 7.2 summarises the mean SF-36 scores at baseline and follow-up. At baseline, the mean SF-36 scores were the highest in the SF domain with a mean of 74.1 ± 31.1, and the lowest in the GH domain with a mean of 56.0 ± 24. For the follow-up phase, the highest score was reported for the MH with a mean of 76.0 ± 18.0, and the lowest for the RP with a mean of 57.3 ± 42.6.

The SF-36 subscale mean difference between baseline and follow-up reported no statistically significant changes, indicating stability in overall QoL during the study period. However, slight variations were observed across specific domains. Positive mean differences found in the PF, RP, RE, VT, and SF subscales suggesting a worsening outcome at follow-up. In contrast, negative mean difference was observed in the MH, BP, and GH subscales, indicating an improvement in these domains at follow-up.

Table 7.2 SF-36 subscales at baseline and at six months follow-up phases

	Baseline		6 months follow up			
SF-36 Domains	**Mean**	**Range**	**Mean**	**Range**	**Mean diff., (95% CI)**	**p-value**
PF	69.7	(0-100)	67.1	(0-100)	2.6 (-14.2 to 19.4)	0.75
RP	61.9	(0-100)	57.3	(0-100)	4.5 (-20.2 to 29.2)	0.71
RE	66.3	(0-100)	62.1	(0-100)	4.1 (-20.7 to 29.0)	0.73
VT	63.0	(20-95)	59.7	(15-100)	3.2 (-10.5 to 17.1)	0.63
MH	72.2	(25-100)	76.0	(48-100)	- 3.8 (-16.3 to 8.7)	0.54
SF	74.1	(12-100)	69.0	(0-100)	5.0 (-12.5 to 22.7)	0.56
BP	62.0	(0-100)	65.7	(0-100)	- 3.6 (-20.6 to 13.2)	0.66
GH	56.0	(10-100)	61.2	(0-100)	- 5.2 (-20.8 to 10.3)	0.49

Abbreviations; 95% CI; 59% confidence interval for the mean difference between the values of the domains at baseline and six-months follow-up. Mean diff.; means differences. SF-36; 36-item short form health survey. PF; physical functioning. RP; role-limited to physical health. RE role-limited to emotional problems. VT; vitality. MH; mental health. SF; social functioning. BP; bodily pain. GH; general health.

7.5.2.1 SF-36 of females vs. males

Five females were diagnosed with monostotic FD, five with polyostotic FD, and one with MAS. In males, six were diagnosed with monostotic FD, and four were diagnosed with polyostotic FD. Males scored higher across all SF-36 subscales compared with females. The difference in SF-36 subscale scores between males and females was reported from the highest to the lowest as follows: RE (84.3 vs. 50), PF (82 vs. 58.6), SF (82.5 vs. 66.5), VT (71 vs. 55), MH (80.2 vs. 65), RP (69.5 vs. 55), BP (67.5 vs. 57), and GH (59.5 vs. 52.8), as shown in Figure 7.1. The greatest difference between sexes was found in the RE domain, with a difference of 45.7 points in baseline and 31.4 points in follow-up phases between the mean scores (Figure 7.1).

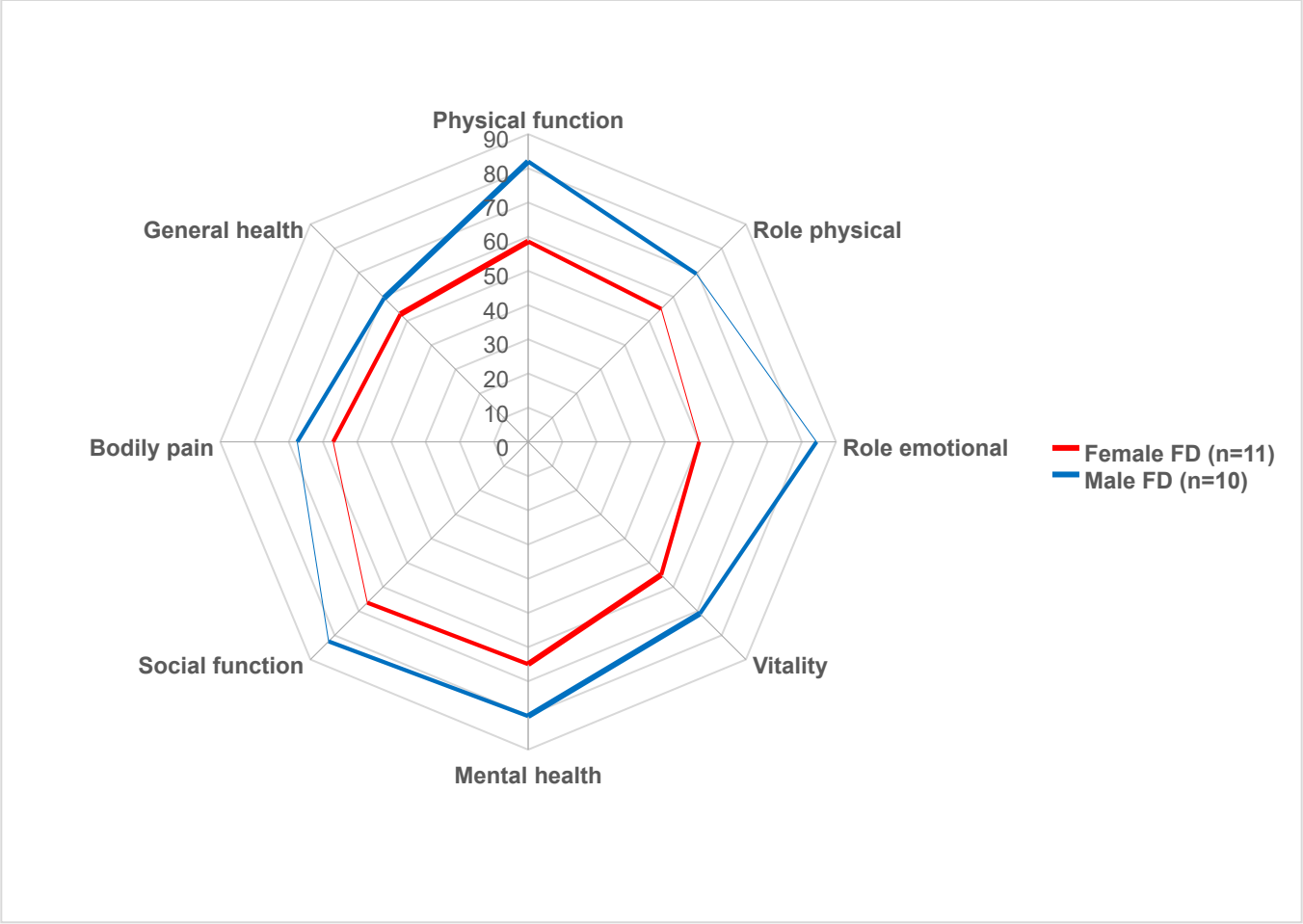


Figure 7.1 Radar plot of the SF-36 subscales of females and males with fibrous dysplasia

7.5.2.2 Monostotic FD vs polyostotic FD

Patients with polyostotic FD had lower SF-36 scores than those with monostotic FD: PF (63.3 vs. 74.5), RP (50.5 vs. 72.2), RE (66.8 vs. 71.9), VT (57.9 vs. 69.8), MH (67.6 vs. 78.9), SF (64.7 vs. 82.9), BP (58.6 vs. 66.13), and GH (51.7 vs. 60.04).

The RP and SF domains had the greatest difference between the reported scores of monostotic FD and polyostotic FD. (22, and 18.2, respectively). The remaining domains had an average of 11 points difference. The lowest difference was observed in the RE scores (5.1 points) (Figure 7.2).

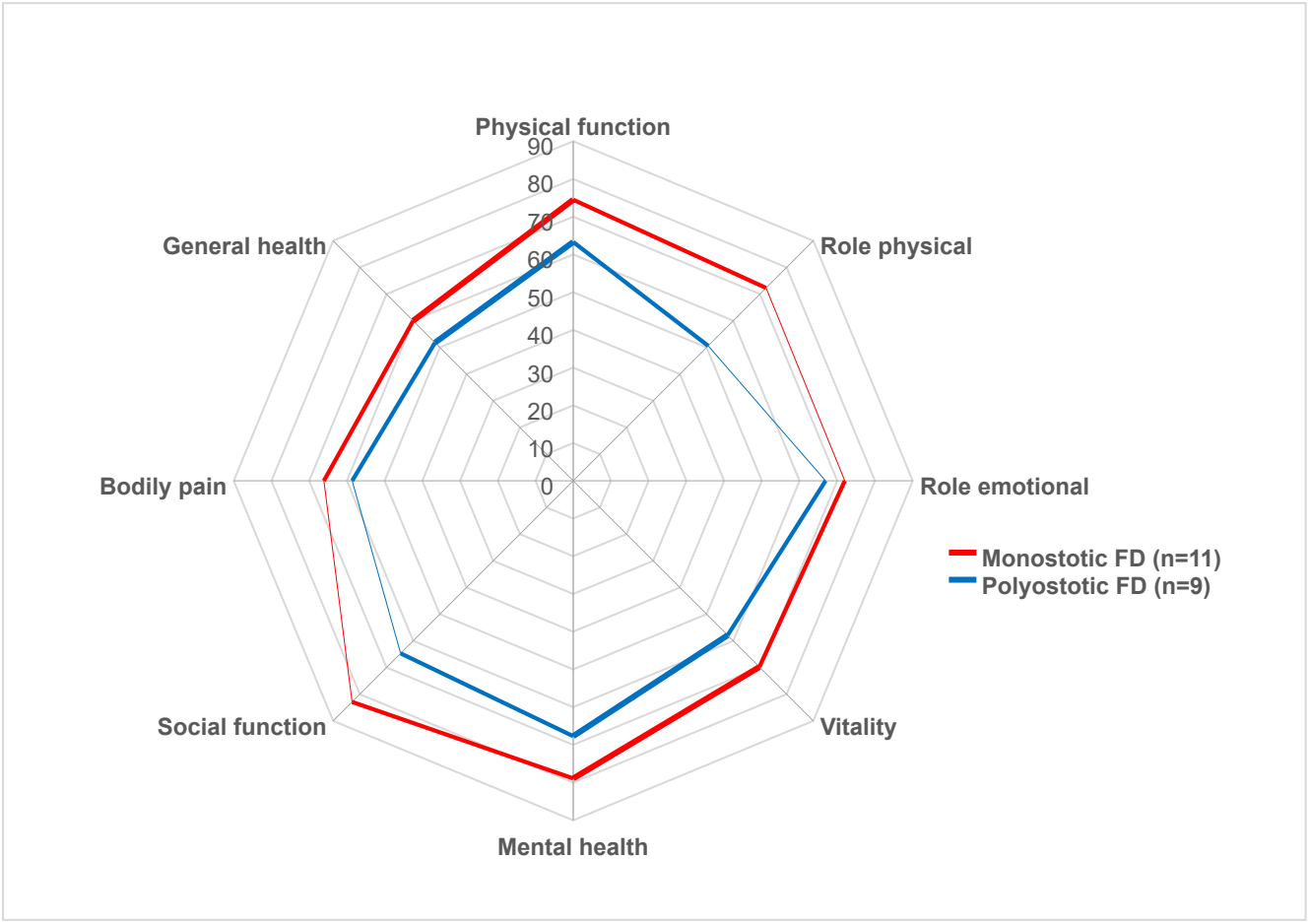


Figure 7.2 Radar plot of the SF-36 subscales of monostotic FD and polyostotic FD

7.5.3 Measured bone pain

The mean pain intensity, worst, current, and average pain scores at baseline were 3.1, 3.5, 3.3, and 3.0, respectively. At the follow-up phase, pain intensity, worst, current, and average pain scores were 2.6, 3.0, 3.0, and 2.7, which were slightly lower than baseline. The reported pain intensity for the baseline and follow-up is categorised as mild pain. The baseline values for the pain interference phase are 1.9 and 2.3 for the follow-up phase. The dimension with the highest pain interference at baseline was mood, with a mean 3.1 ± 3.6, followed by sleeping, with a mean of 3.0 ± 3.2. At follow-up, normal working 2.5 ± 3.0 and walking ability 2.4 ± 3.1 dimensions scored the highest pain interference. When comparing the pain interference scores at baseline and follow-up, pain interference, general, walking ability, and normal work scores increased at baseline and follow-up, while mood, relationships with others, sleep, and enjoyment of life decreased at follow-up.

Table 7.3 summarises the differences between the BPI scores at baseline and follow-up. In all dimensions, there was a positive change in pain intensity. There were positive and negative changes for pain interference. There is weak evidence of improvement ($p = 0.06$) in the mood dimension. Figure 7.3 illustrates the pain location map; the skull, followed by the right and left legs and knees, reported greater pain intensity than other parts of the body.

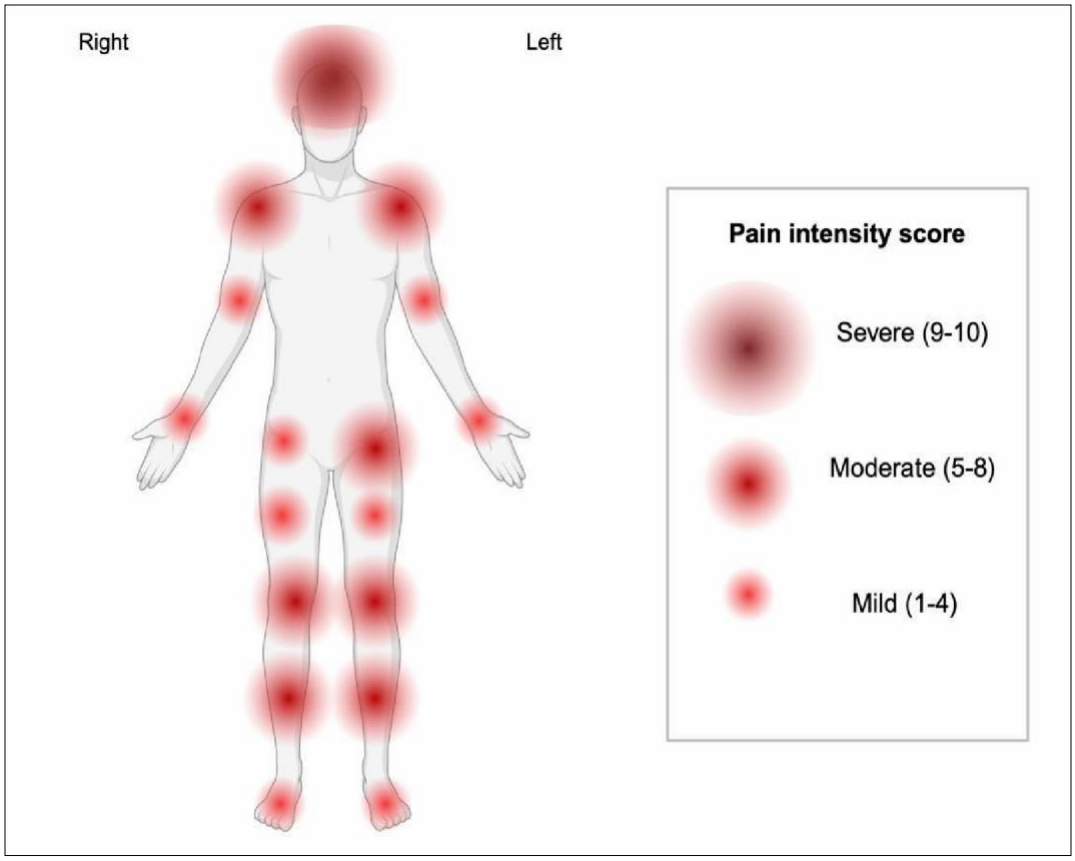


Figure 7.3 The distribution of the reported pain locations

The size and the shade of the radial gradient represent the severity of the reported pain. The skull area has the highest reported pain severity followed by the legs, knees and the left pelvis. Other pain locations were considered as a mild pain.

Table 7.3 The BPI scores of patient cohort at baseline and follow-up

	Baseline		6 months Follow-up			
BPI dimension	mean	Range	mean	Range	Mean diff. (95% CI)	p-value
Pain intensity	3.1	(0-9.75)	2.6	(0-10)	0.45 (-1.19 2.09)	0.58
Worst pain	3.5	(0-10)	3.0	(0-10)	0.47 (-1.52 2.47)	0.63
Average pain	3.0	(0-10)	2.7	(0-10)	0.28 (-1.58 2.15)	0.75
Current pain	3.3	(0-10)	3.0	(0-10)	0.28 (-1.70 2.27)	0.77
Pain interference	1.9	(0-6.85)	2.3	(0-7.14)	0.37 (-0.99 1.74)	0.58
General activity	2.0	(0-8)	2.3	(0-10)	-0.33 (-1.94 1.27)	0.67
Mood	3.1	(0-10)	1.4	(0-8)	1.71 (-0.13 3.56)	**0.06**
Walking ability	1.7	(0-8)	2.4	(0-10)	-0.71 (-2.55 1.12)	0.43
Normal work	2.3	(0-9)	2.5	(0-9)	-0.19 (1.97 1.59)	0.83
Relationships with others	1.6	(0-8)	1.2	(0-9)	0.38 (-1.39 2.15)	0.66
Sleeping	3.0	(0-10)	2.2	(0-10)	0.80 (-1.13 2.75)	0.40
Enjoyment of life	2.3	(0-9)	1.3	(0-10)	0.95 (-0.81 2.71)	0.28

Abbreviations; BPI, brief pain inventory, 95% CI, 95% confidence interval. Mean diff, the mean difference between baseline and follow-up.

7.5.3.1 Comparison of BPI in females vs. males

Figure 7.4 represents the box-whisker plots for all BPI dimensions for females compared to males in our patient cohort. Females scored higher pain intensity than males (median of 4.27 vs. 1.85). For the worst pain in the last 24 hours, females scored 10, while males scored 5. This also applies to average and current pain dimensions. Pain interference was also higher in females than males (3.09 vs. 1.5). The mood dimension scored the highest in females (median of 4.27, with a maximum of 10), while enjoyment of life scored the highest in males (median of 1.9, with a maximum of 9).

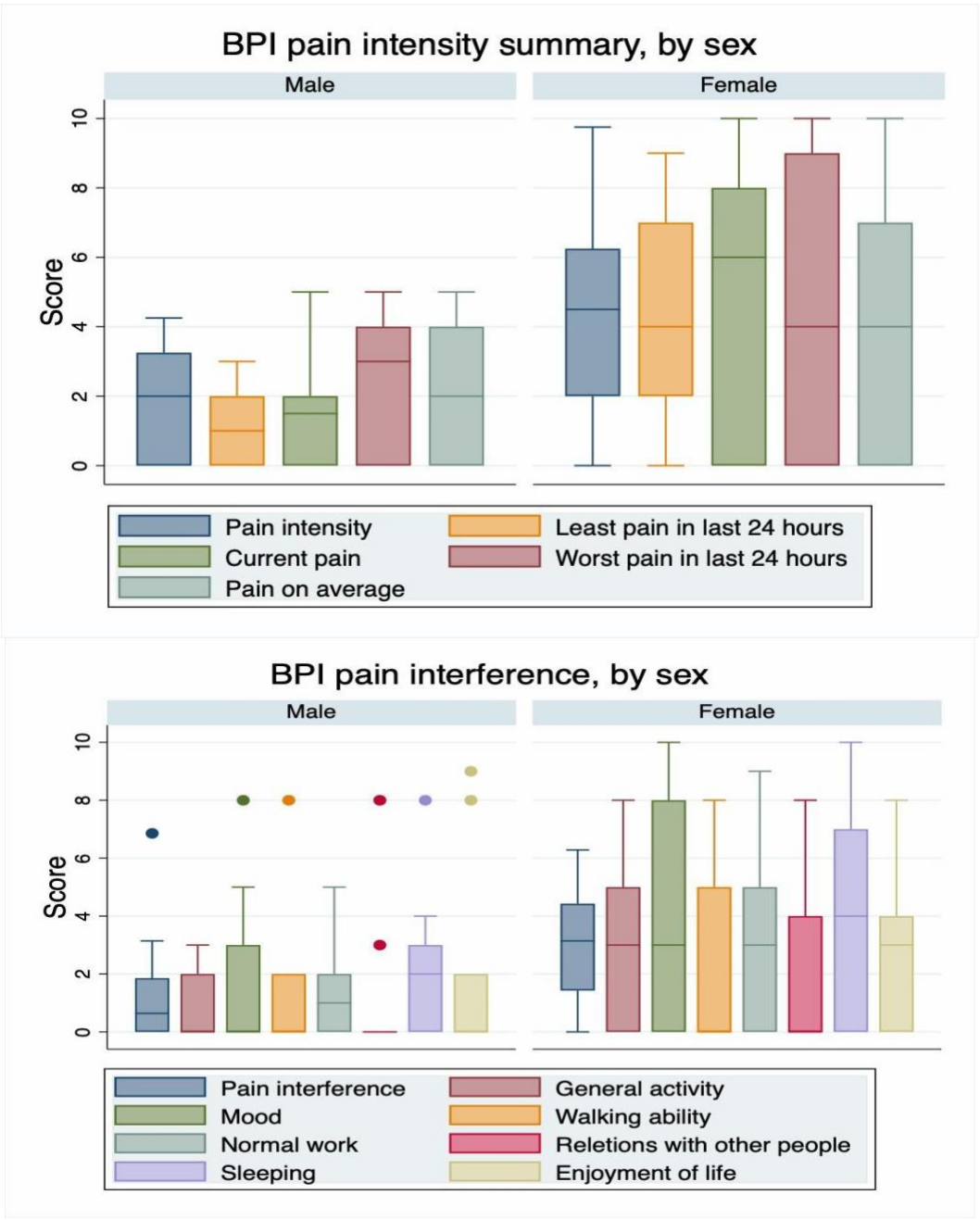


Figure 7.4 Box and whiskers plot of the BPI grouped by sex

The boxes represent the horizontal line represent the median, the box boundaries represent the upper and lower quartile (IQR) of the BPI scores while whiskers represent the maximum and the minimum scores, the dots represent the outliers and are calculated by a formula which varies depending on the UK and USA software. Floor and ceiling effects are seen in the plots. The top plot represents the BPI pain intensity plot. Females experience pain intensity variables and higher median than males. The bottom plot represents the BPI pain interference plot. Females experience greater variability with a similar median in pain interference, general activity, mood, normal work and enjoyment of life. Many outliers in males demonstrated a diverse pain interference score in males.

7.5.3.2 Comparison of BPI between monostotic FD vs polyostotic FD

The mean pain intensity at baseline was the highest in MAS, followed by polyostotic FD and monostotic FD patients, with scores of 6, 3.66, and 3.18, respectively. At follow-up, the pain intensity scores were lower than baseline. The reported scores of MAS patients (n = 1) and monostotic FD patients (n = 11) were similar in the worst pain, least pain, and average pain intensity dimensions. polyostotic FD reported lower scores in all pain intensity dimensions (Figure 7.5).

The scores of pain interference at baseline were high in polyostotic FD patients compared with monostotic FD and MAS, except for the mood dimension, where MAS scored 10. The difference between the scores of polyostotic FD and monostotic FD is small. At follow-up, MAS scored the highest in general activity, mood, and walking ability compared to other FD subtypes. Patients with monostotic FD scored higher pain interference than those with polyostotic FD in the following dimensions: sleep (2.8 vs. 1.8), relationships with others (1.4 vs. 1.2), enjoyment of life (1.7 vs. 1.1), walking ability, and normal work (2.9 vs. 2.4). General health and mood dimensions were higher in polyostotic FD than monostotic FD, with scores of (2.3 vs. 2.0) and (1.8 vs. 0.9), respectively.

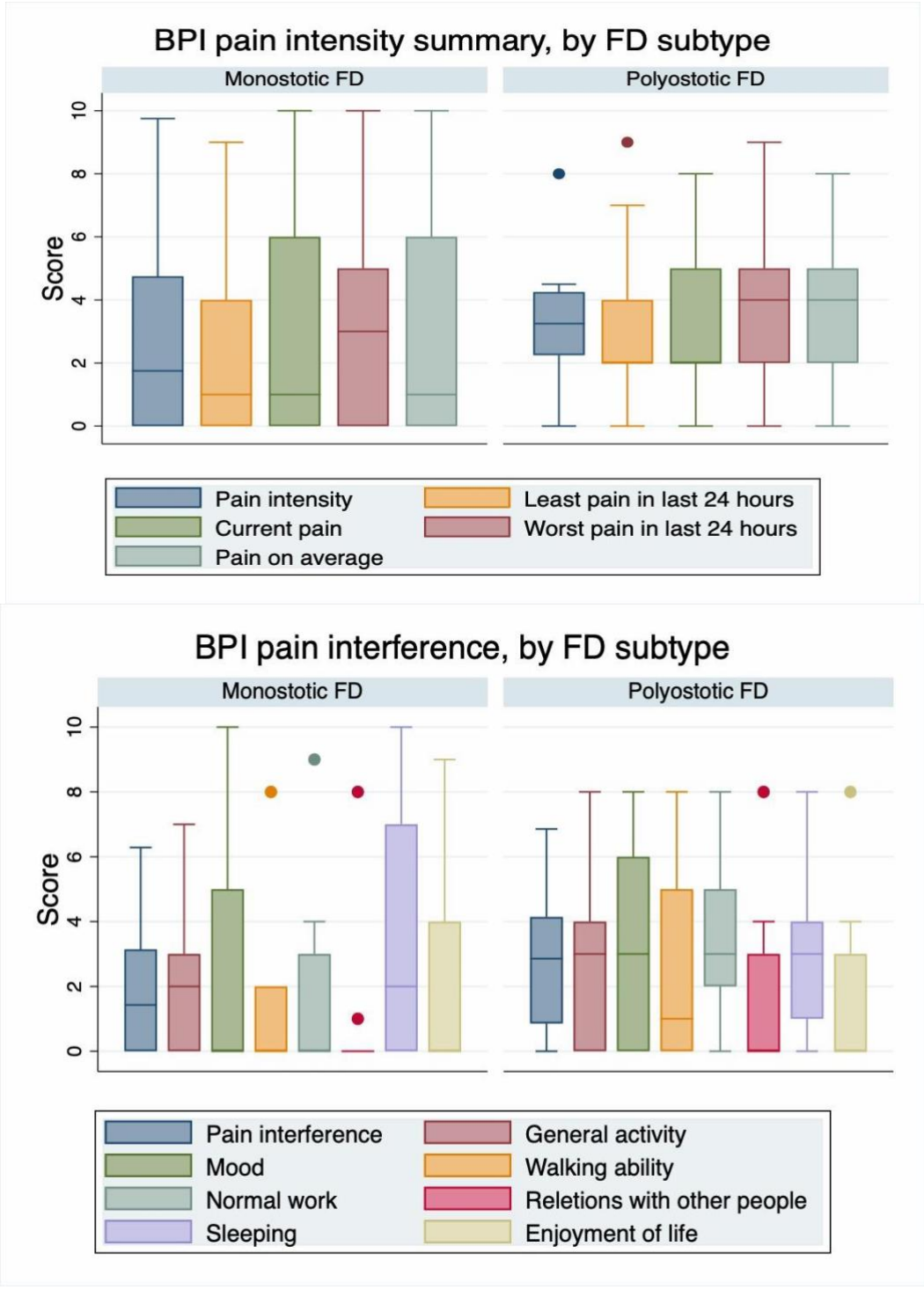


Figure 7.5 Box and whiskers plot of the BPI grouped by the FD subtype.

The top plot represents pain intensity levels. Monostotic FD, pain intensity had higher variability and low median in all dimensions except for the worst pain scored. Polyostotic FD scores were closer to the median with few outliers. the bottom represents the pain interference. Both monostotic FD and polyostotic FD have outliers and the pain interference scores were diverse.

7.5.4 Correlation analysis

Ambulatory status was found to be moderately associated with the SBS_{total} (r = 0.68, p=0.10) and $SBS_{(legs + pelvis)}$ (r = 0.62, p=0.06). Patients with polyostotic FD were strongly associated with ambulatory status, SBS_{total} (r = 0.80), and $SBS_{(legs + pelvis)}$ (r = 0.90). No association was found between the measurement of ALP levels with SBS_{total} (r = 0.12) nor $SBS_{(legs + pelvis)}$ (r = 0.10).

7.5.4.1 Correlation SBS with physical component of SF-36

At baseline, there was no relationship between the SBS_{total} or $SBS_{(legs + pelvis)}$ with any of the SF-36 domains. At follow-up, the Pearson's correlations were stronger across all SF-36 domains, but not significant, except for a moderate relationship between the $SBS_{(legs + pelvis)}$ and the RP domain (r = -0.5, p= 0.02), and a weak correlation with the RP domain and SBS_{total} (r = -0.32, p=0.14) (Table 7.4).

Correlation was measured across FD subtypes; in patients with monostotic FD, there was no correlation between the SBS_{total} and any of the SF-36 domains. $SBS_{(legs + pelvis)}$ was moderately correlated with RP (r = -0.50, p=0.02), and weakly correlated with PF (r = -0.27), and BP (r = -0.35) at follow-up in monostotic FD patients. In the polyostotic FD group, the total SBS showed weak correlations with the RP (r = -0.40), PF (r = -0.32), and GH (r = -0.25) domains at baseline. And with the RP (r = -0.49), GH (r = -0.39), and PF (r = -0.20) domains at follow-up. $SBS_{(legs + pelvis)}$ demonstrated moderate correlation with RP at baseline (r = -0.40). And GH (r = -0.60) and RP (r = -0.56) at follow-up. The $SBS_{(legs + pelvis)}$ demonstrated a weak correlation with PF (r = - 0.36), BP (r = - 0.30), GH (= -0.25), and at the follow-up, PF (r = -0.37) and BP (r = - 0.25).

Table 7.4 Pearson's correlation between SBS $_{total}$ and SBS $_{(legs + pelvis)}$ and SF-36 domains at baseline and follow-up

SF-36 domain	SBS $_{total}$		SBS $_{(legs + pelvis)}$	
	Baseline	Follow up	Baseline	Follow up
PF	- 0.05 (0.80)	- 0.06 (0.77)	- 0.13 (0.57)	- 0.29 (0.19)
RP	- 0.13 (0.57)	- 0.32 (0.14)	- 0.18 (0.43)	**- 0.5 (0.02)**
RE	0.02 (0.90)	- 0.16 (0.48)	0.07 (0.74)	-0.31 (0.16)
VT	-0.12 (0.58)	0.19 (0.38)	-0.23 (0.29)	-0.08 (0.71)
MH	-0.03 (0.86)	0.09 (0.68)	-0.13 (0.54)	-0.18 (0.41)
SF	0.08 (0.70)	0.15 (0.50)	0.14 (0.52)	0.01 (0.93)
BP	0.0 (0.97)	- 0.05 (0.82)	- 0.02 (0.92)	- 0.24 (0.28)
GH	- 0.12 (0.57)	- 0.14 (0.53)	- 0.15 (0.50)	- 0.29 (0.19)

Abbreviations; SF-36; 36-item health survey. PF; physical functioning. RP; role-limited to physical health. RE role limited to emotional problems. VT; vitality. MH; mental health. SF; social functioning. BP; bodily pain. GH; general health. Pearson's correlation r, and the significance, (p-value). The values in bold represent a moderate Pearson's correlation.

7.5.4.2 Correlation SBS with BPI

A high $SBS_{(legs + pelvis)}$ is associated with greater pain interference at follow-up. In addition, Interference in relationship with others (r = 0.63), enjoyment of life (0.61), walking ability (r = 0.51), average pain interference (r = 0.5), and mood (r = 0.47). A similar relationship was also found between SBS_{total} and mood (r = 0.63), enjoyment of life (r = 0.51), and relationships with others (r = 0.47). When comparing the association across FD subtypes, patients with monostotic FD, no association was shown between the SBS_{total} and BPI pain interference sections at baseline. At follow-up, the following dimensions demonstrated moderate association: mood (r = 0.71), enjoyment of life (r = 0.61), and relations with others (r = 0.50).

When assessing $SBS_{(legs + pelvis),}$ moderate association was shown in the following dimensions: relationship with others (r = 0.84), enjoyment of life (r = 0.81), mood (r = 0.51), and walking ability (r = 0.50). Patients with polyostotic FD demonstrated a moderate association between SBS_{total} and mood (r = 0.69), walking ability (r = 0.64), enjoyment of life (r = 0.63), and relationships with others (r = 0.57), at the follow-up phase. Also, a moderate association was found between $SBS_{(legs + pelvis)}$ and mood (r = 0.60), walking ability (r = 0.60), general activity (r = 0.51), and enjoyment of life (r = 0.46) dimensions at follow-up. There was no correlation between SBS and pain intensity dimensions in the total patient cohort or across any FD subtypes.

7.5.4.3 Correlation SF-36 with BPI

An impairment of the PF domain of SF-36 demonstrated a moderate association with higher scores of about all the BPI dimensions: least pain (r = 0.77), pain intensity (r = 0.64), average pain (r = 0.64), worst pain (r = 0.48), and current pain (r = 0.47). A strong relationship was observed with the normal work dimension (r = -0.91). Moderate relationship between average pain interference (r = -0.75) and walk ability (r = -0.70).

7.5.5 Factors associated with SBS in multivariable linear regression

The relationship between SBS $_{(legs + pelvis)}$ and RP at follow-up was examined using linear regression analysis. Our study aimed to determine the extent to which RP at the followup months could be explained by SBS $_{(legs + pelvis)}$. The explained variation ranges from 0 to 1 and is denoted as r^2. Sex was considered a covariate, other covariates, such as age and ALP, could not be incorporated due to the limited sample size (n = 21). Additionally, SF-36 domains other than RP were not considered, as the correlation coefficients showed no obvious linear relationships. Regression revealed a statistically significant relationship (F (1,19) = 6.27, p = 0.021), with SBS $_{(legs + pelvis)}$ accounting for 24.8% of the explained variability in RP at follow-up.

These results were significant at the p<0.001 level. The regression equation is as follows:

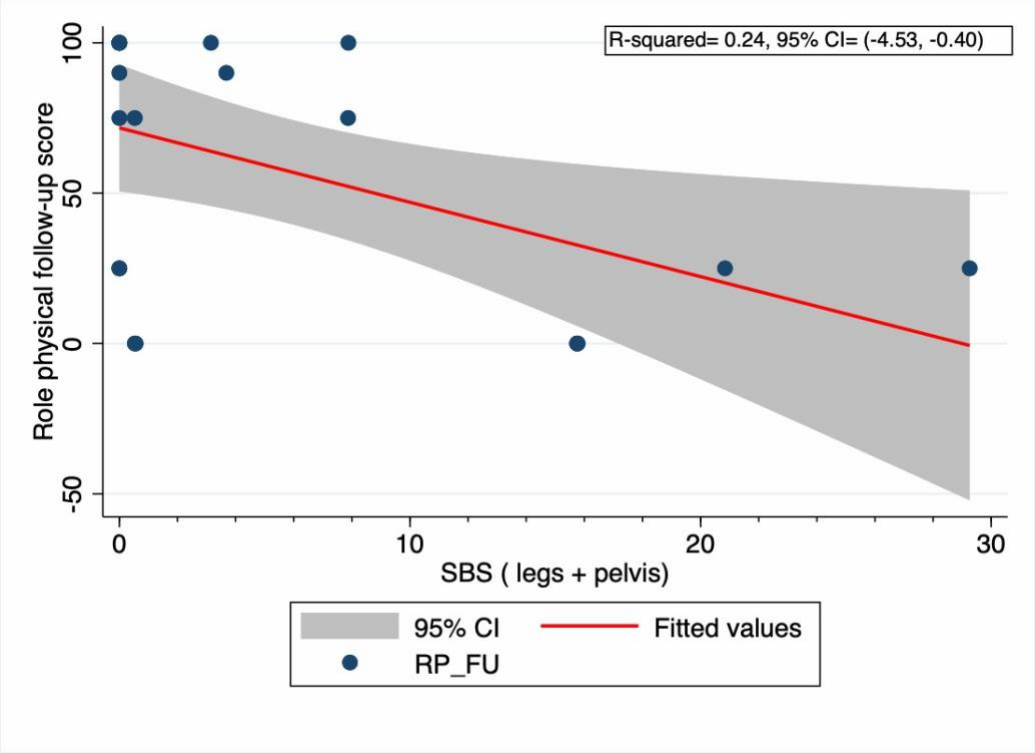
$$\textbf{Predicted RP} = 71.69 - (2.47 * SBS_{(legs + pelvis)})$$

Each additional score of SBS $_{(legs + pelvis)}$ was associated with a decrease on average of 2.47 points in the RP SF-36 domain at follow-up (Figure 7.9, a).

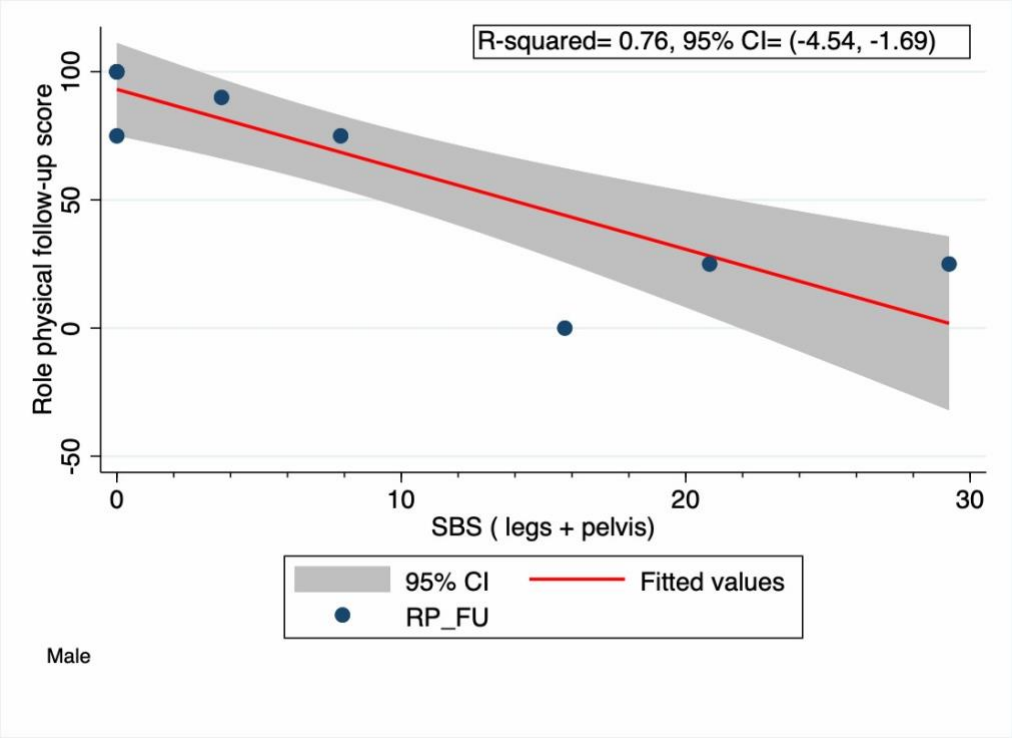
Multiple linear regression was conducted to predict RP from SBS $_{(legs + pelvis)}$ and sex, which proved to be statistically significant for the predicted RP ($F(2,18) = 5.934$, $p < 0.05$). SBS $_{(legs + pelvis)}$ and sex collectively accounted for 39.7% of the variance in RP at the follow-up. All the variables were found to be statistically significant ($p < 0.001$). Male sex was a significant contributor to a lower role limitation due to physical health problems ($F(1,8) = 25.42$, $p < 0.001$), accounting for 76% of the variability in males and SBS $_{(legs + pelvis)}$ (Figure 9, b).

On the other hand, the regression model that tried to predict RP at follow-up came up with ($F(1,9) = 1.05$, $p = 0.33$), which explained only 10% of the variation in females and SBS $_{(legs + pelvis)}$ (Figure 9, c). An additional analysis was carried out by the PF, which confirmed a strong relationship in males and not in females. To predict the PF domain SF-36 at follow-up, a regression analysis was performed using SBS $_{(legs + pelvis)}$ and sex. The results ($F(2,18) = 2.02$, $p = 0.16$) indicated 18.3% variability in SBS $_{(legs + pelvis)}$ and sex. In males, predicting PF follow-up ($F(1,8) = 11.21$, $p<0.01$) accounted for 58.3% of the variability with SBS $_{(legs + pelvis).}$ No linear correlation was found in females ($p = 0.81$).

a)


R-squared= 0.24, 95% CI= (-4.53, -0.40)
Role physical follow-up score
100
50
0
-50
0
10
20
30
SBS (legs + pelvis)
95% CI
Fitted values
RP_FU

b)


R-squared= 0.76, 95% CI= (-4.54, -1.69)
Role physical follow-up score
100
50
0
-50
0
10
20
30
SBS (legs + pelvis)
95% CI
Fitted values
RP_FU
Male

c)

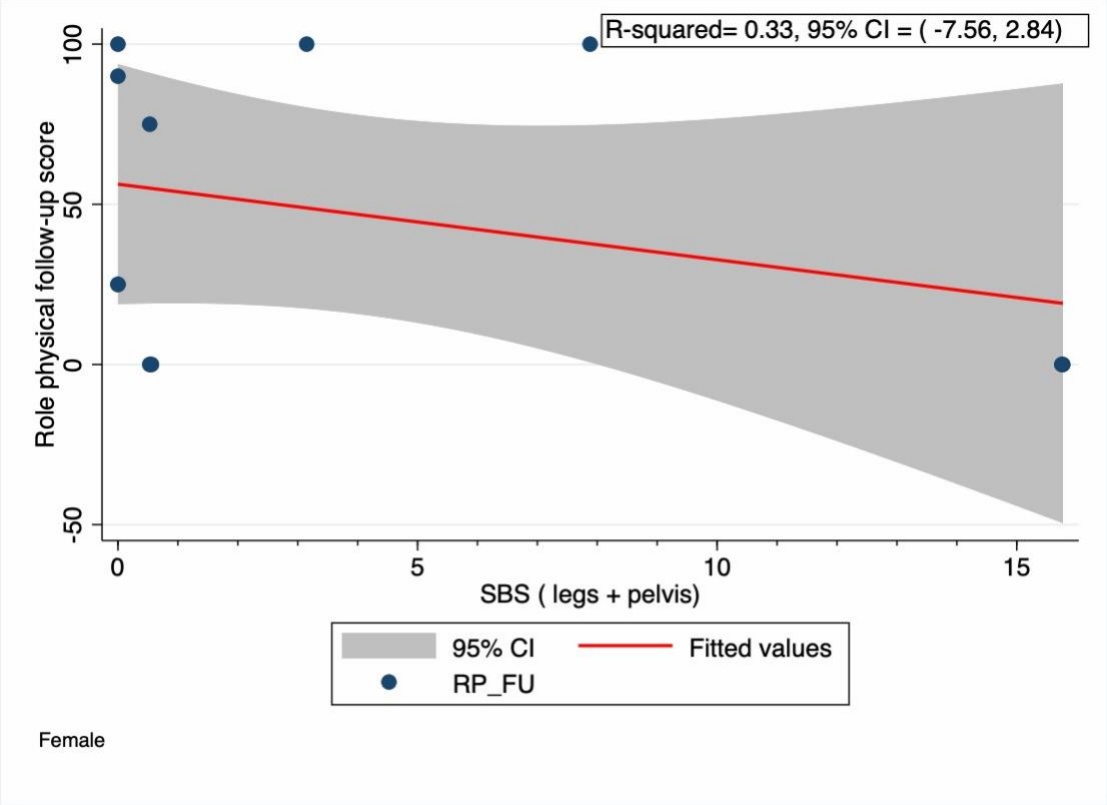


Figure 7.6 Simple linear regression analysis between SBS (legs + pelvis) and the RP SF-36 domain at follow-up (first panel, a), in males (second panel, b) and in females (third panel, c).

The grey area represents the 95% CI of the regression line (red), observations are the dots in dark blue. RP, role limited to physical health. Observations within the confidence interval (grey area) influence the R2 but not the regression model.

7.5.6 Regression diagnostics

7.5.6.1 Residuals plots

The purpose of performing residual plots from the regression analysis is to examine the assumption of residuals from the regression model is normally distributed. The residual is the difference between the raw data and the predicted data from the regression equation [21, 22]. Ideally, histograms of the residuals should follow an approximate normal distribution of a bell-shaped curve. For a perfect normal distribution, the following relationships hold true: mean ± 1 SD equals 68% of the data; mean ± 2 SD equals 95% of the data. Figure 7.7 demonstrates the residual plots of the regression analysis. Neither plot showed a normal distribution, but the left-side histogram, the one with sex variable included, showed a tighter residual distribution with an almost bell-shaped curve, skewed to the right. On the other hand, the right-side histogram (without sex variable), showed asymmetric curve with a residual distribution far away from the regression model.

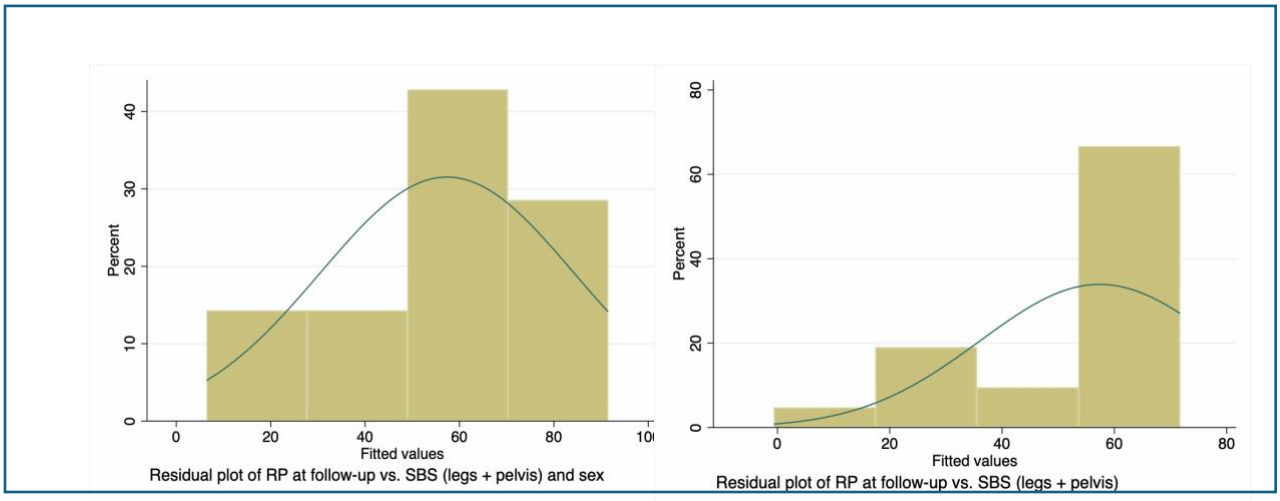


Figure 7.7 Histogram of residuals.

Right hand side plot shifts to the left. Left hand side appears more than normal after including sex. The black lines are plotted from the observed means and standards deviations.

7.5.6.2 Regression towards the mean

We conclude the regression analysis with the concept of regression towards the mean, which was first introduced by Francis Galton in 1886 [23]. Regression towards the mean is a statistical phenomenon that occurs due to the natural variability of the variables in regression. It occurs when the first measurement of a variable is extreme, and the second measurement tends to be closer to the mean. We performed regression towards the mean of the PF domain scores of our patient cohort (Figure 7.8).

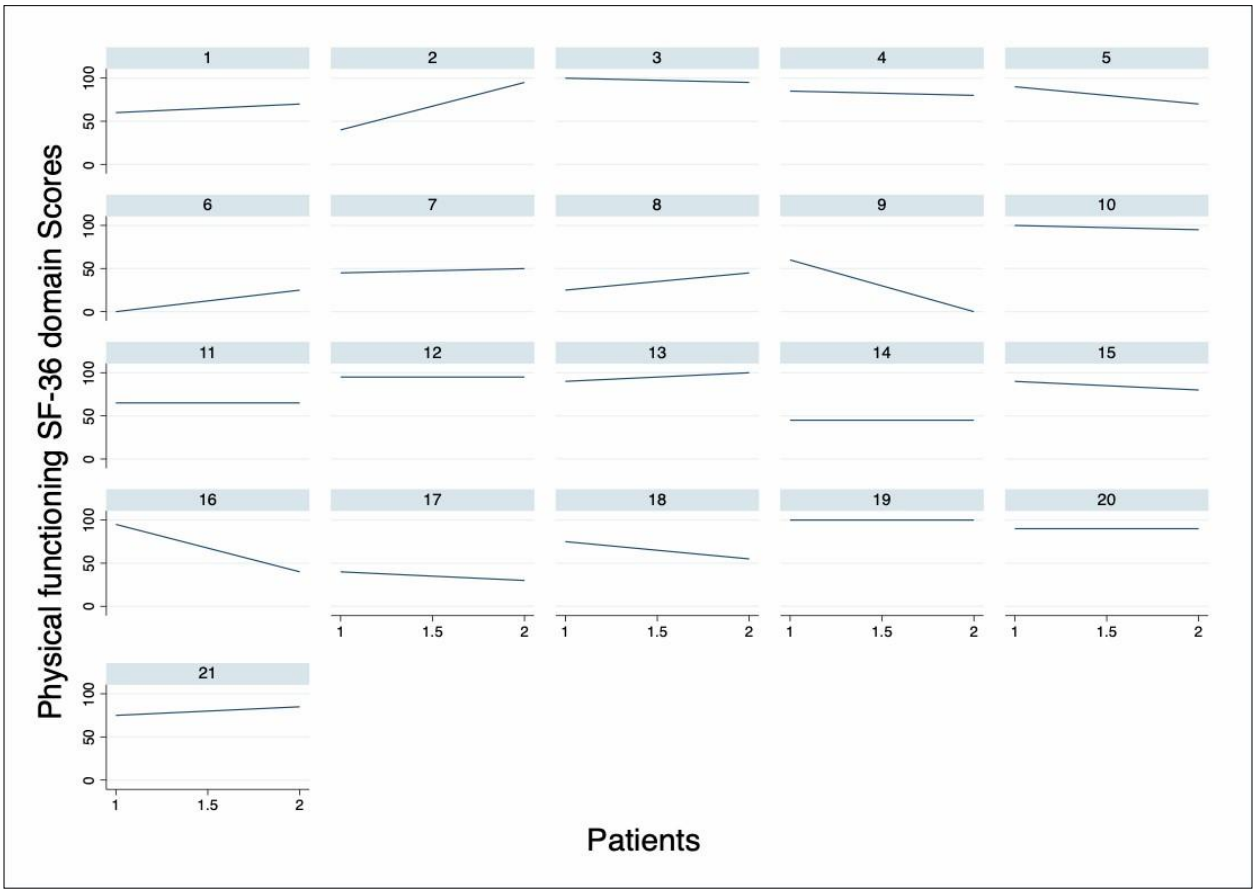


Figure 7.8 Regression towards the mean.

Patient ID 2,9 and 16 are illustrations. Patient ID 16 dropped from 95 to 45 of PF domain. In contrast, patient ID 2 increased from 45 to 100 of the same domains. Patient ID 9 dropped from a lower base.

7.6 Discussion

The aim of this study was to evaluate the QoL of patients with FD/MAS in Saudi Arabia and to investigate the relationship between skeletal burden with the physical component of QoL. This study adhered to the international FD/MAS guidelines [5] and utilised the SF-36 instrument for QoL evaluation and the BPI for pain assessment. Also, we assessed the FD skeletal involvement using SBS to measure the SBS_{total} and $SBS_{(legs+ pelvis)}$. Previous studies have shown that FD has a significant impact on QoL and physical abilities. Studies have also found that the presence of bone pain is associated with lower QoL scores [4, 7, 9]. Despite the international FD/MAS recommendations and the literature findings, QoL in FD/MAS patients from Saudi Arabia has not been investigated before. Therefore, our study sought not only to measure QoL and bone pain but also to evaluate the relationship between SBS with the SF-36, BPI, ALP levels and ambulatory status. We hypothesised that the $SBS_{(legs + pelvis)}$ would have a stronger correlation with the physical domains of SF-36 than the SBS_{total}, implying that FD involvement in the lower extremities and pelvic areas directly influences ambulation and physical functioning. This notion was inspired by a study by Hart et al. [10], which found that the FD involvement of the lower extremities, pelvis, and spine areas was linked to functional and ambulatory status. However, we didn't include spinal subregion assessments in the SBS calculations, as we believe that FD lesions in the spine are not weight-bearing and do not signify functional or ambulatory status.

The first outcome of our study was to evaluate the QoL of our patient cohort's. We found that the scales reflected physical health (PF, RP, BP, and GH) had a mean score of 62.4, while the scales that reflected mental health (RE, VT, MH, and SF) had a mean score of 68.9. This small distinction between physical and mental health highlights how even mild manifestations of FD can have an adverse effect on physical health. This finding is consistent with that of Kelly et al. [7], who measured the QoL of patients with FD and revealed that physical domains were significantly affected, whereas the scores of mental domains were similar to the scores of the American reference standard In the same way, Majoor et al. [9] found that the FD/MAS patient group had lower QoL scores than the Dutch reference standard across all domains except the MH and RE scales. Moreover, this is the first study to measure the QoL of patients with FD from Saudi Arabia; however, a study by Abdulrashid et al. [24] measured the SF-36 of healthy individuals and correlate the scores with the physical activity in Saudi Arabia. The findings were that the SF-36 scores of physically inactive individuals were similar to our patient cohort scores. The physical activity was measured by using the general practice physical activity questionnaire. This might indicate that the physical functioning of our patient cohort is impaired compared with general population.

At follow-up, SF-36 declined in the PF, RP, RE, VT, and SF domains, suggesting subtle changes in patient-reported QoL over time. Such fluctuations may be attributed to a variety of factors, including treatment adaptations, disease progression, incident fractures, shifts in lifestyle, social, and psychological statuses. However, our patients reported no change over the six-month follow-up period, indicating that the fluctuation could be caused by external factors unrelated to FD. Patients with polyostotic FD

experienced more pronounced QoL impairment across all SF-36 domains than those with monostotic FD, particularly in the RP and SF domains. This finding is in line with earlier research that showed that more extensive FD, like polyostotic FD and MAS, is linked to a worse quality of life than monostotic FD. This is because polyostotic FD is more likely to be linked to complications like bone pain and pathological fractures than monostotic FD [8, 9, 25, 26].

The RP domain was moderately correlated with $SBS_{(legs + pelvis)}$ ($r = - -0.5$, $p = 0.02$), weakly correlated with the PF domain ($r = -0.29$, $p = 0.19$), and showed no correlation with other SF-36 domains. This finding was contrary to previous studies, which suggested a correlation between total SBS with the PF domain ($r - -0.51$, $p<0.001$) [9] , and ($r = -0.43$, $p = 0.009$) [7], but not a significant correlation with the RP domain ($r = 0.18$, $p = 0.17$) [9]. The reason for these differences may be related to the mean SBS of our patient cohort, which was 6.43 SBS_{total} and 5.78 $SBS_{(legs + pelvis)}$, compared to the reported mean SBS of 31 in other studies [7], which is five times higher than our calculated SBS_{total}. Severe skeletal burden is linked to strong and pronounced impairment in the physical domains of SF-36. Additionally, the RP and PF of our patient cohort were significantly correlated ($r = 0.7799$, $p<0.0001$). To our knowledge, no study has reported using SBS for specific segments to assess its relationship with SF-36 domains.

The second outcome of our study revealed that male sex, FD, and high $SBS_{(legs + pelvis)}$ predicted an impaired RP domain of SF-36, which accounted for 76% of the variance in the RP scores. This relationship wasn't seen in the female group due to the variation of the SF-36 scores. On the contrary, previous studies demonstrated a predicted PF domain scores in females ($\beta = -17.6$; $p = 0.002$), with high SBS ($\beta = -1.08$; $p < 0.001$), and high

bone marker turnover; fibroblast growth factor-23 (FGF-23), and procollagen 1 N-terminal propeptide (PINP) as significant predictors for impaired the PF domain [9].

Pain is the most reported complication arising from FD/MAS, affecting an estimated 81% of adults [4, 27]. In our study, we used BPI to assess pain. The reported a mean worst pain of 3.5, least pain of 2.6, average pain of 3.0, and current pain of 3.3, categorising the pain as mild. The pain intensity was greater in the skull followed by the lower extremities and both knees. Pain intensity was greatest in our single patient with MAS, followed by those with polyostotic FD, and was lowest in those with monostotic FD. A study by Spencer et al. [27], demonstrated greater pain reports amongst polyostotic FD patients compared to their monostotic FD counterparts. However, another two studies reported greater pain in monostotic FD compared to polyostotic FD, contributing to the complex nature and mechanisms of pain in FD [4, 28]. Previous studies have attempted to understand mechanism of pain derived from FD and found that pain can be either nociceptive or neuropathic, with each type being treated differently [27, 29]. Pain is also found to be influenced by the location of the FD lesion, age changes, and the individual's sex [28]. Patients with polyostotic FD had greater pain interference compared to those with MAS and monostotic FD in the following dimensions: normal work, walking ability, relationships with others, sleep, mood, and enjoyment of life. Interestingly, the mood dimension of patients with polyostotic FD were significantly correlated with SBS total ($r= 0.69$, $p=0.03$). In contrast, Majoor et al. [9] showed no association between SBS and BPI. This differs from the findings presented here, and the reason for this discrepancy might be related to the amount or the type of pain reported by our patient cohort Future studies should evaluate pain in FD/MAS to further understand the physiology of it.

Another intriguing finding was that females had more pronounced QoL impairment compared to males. Females showed a significantly greater impairment in the RE domain compared to males, suggesting that emotional problems are negatively impacting their quality of life. This trend was also observed in females' assessments of pain using BPI, where the mood dimension scored the highest with greater variation in pain scores, indicating a significant mood interference due to pain. The reasons behind these sex differences are not clear. Given the equal number of males and females in our sample, as well as the equal distributions of age and FD subtype between sexes, sex bias is unlikely. However, possible external factors influencing the observed differences in pain and QoL between females and males could include biological, psychological, social, and cultural factors [30].

Understanding the difference in perceptions and sensitivity between sexes in FD/MAS patients has been the focus of many studies. [4, 26-28]. Our findings also supported the findings reported by Almalki et al. [31], who assessed chronic pain in Saudi Arabia in a large cohort and demonstrated that females and the elderly suffered more from pain than other study groups. Additionally, they reported that the location of chronic pain was more prevalent in the lower extremities, likely due to the weight-bearing nature of these areas, which increases the risk of pain and fractures [4]. Females in our patient cohort reported greater pain severity and interference than males. This outcome contrasted with the findings of Majoor et al. [4], and Kelly et al. [12], who found no significant difference in pain severity between the sexes. The difference in pain sensitivity and response between sexes has been the focus of much research. A possible explanation for our findings is that females in our cohort scored low on the RE of SF-36, with mood greatly interfered with

by pain associated with FD lesions. Females' higher sensitivity to pain may explain why it interferes more with mood and role limitations due to emotional problems [31]. the BPI is designed to assesses pain in the last 24 hours, leading to some diversity in baseline and follow-up scores and their correlations. This distinction is crucial for interpreting BPI results, and therefore BPI scores should be carefully considered when assessing disease progression.

About 71.4% of our cohort were ambulating independently, while 28.6% required the use of ambulatory assistance aids such as crutches, canes, and wheelchairs. Individuals who ambulated independently had a mean SBS of 5.56, while those who used crutches or canes had a mean SBS of 17, and those who used wheelchairs had a mean SBS of 29.2. This finding demonstrated that a higher SBS_{total} is associated with greater reliance on ambulatory assistance ($r = 0.68$, $p<0.000$) and $SBS_{(legs + pelvis)}$ ($r = 0.62$, $p<0.002$). This relationship was also reported by Collins et al. who documented a correlation between SBS and ambulatory status ($p<0.001$), and by another study [10], which reported a similar correlation ($p<0.0001$).

The measurement of ALP levels is used to measure the metabolic activity of FD and track the progression of FD/MAS. However, our results showed that ALP and SBS did not have a significant relationship with any outcome measures. This is different from what other research has found, which is that ALP and SBS do have a positive relationship (Spearman rho = 0.62) [6]. Similarly, Majoor et al. [9] used ALP as a prognostic tool for the assessment of bisphosphate treatment, which showed a correlation (0.562, $p<0.001$) between SBS and ALP. A plausible explanation for the divergence between our findings and the literature might be the normal range of ALP levels observed within our adult

patient cohort. The strong links between ALP and SBS found in the literature may have something to do with the fact that children were among the patients. This is because ALP levels change with age, reaching their highest levels during childhood when bones are growing quickly and then dropping off as people become adults.

7.6.1 Strength & Limitations

This study represented the first investigation of FD patients in Saudi Arabia, utilising a multicentre approach from large tertiary centres in both the central and eastern regions of the country. One notable strength was the follow-up assessment of QoL and pain, which was conducted at two separate time points. However, the study also had certain limitations, including its small sample size. Patients were reluctant to participate because there were no direct benefits for their current health or care, and many requested medical attentions during the recruitment phase. Another potential reason for the low participation rate could be a lack of motivation or awareness about research. This limitation affected the recruitment of patients with the MAS subtype, resulting in insufficient measurement of QoL and pain.

This study lacks the analysis on the impact of treatment and surgical interventions on QoL and pain outcomes in FD/MAS patients. While the study primarily focused on assessing the relationship between the SBS, QoL and pain, no patients were receiving bisphosphonate therapy or during the QoL and pain assessment period. As bisphosphonates are widely used to manage bone pain in FD/MAS, their potential influence on QoL and pain was not evaluated in this research.

Another limitation was the relatively short follow-up period of six months, which may not be sufficient to capture significant changes in QoL, pain or disease progression in FD/MAS. These conditions often exhibit slow disease progression which is more evident over longer timeframe. The six months duration was selected due to the time constraints of PhD studies, which necessitated a short study period. While this limited timeframe provides insights into short-term outcomes, it also serves the first building block for future longer-outcomes.

Research on QoL of Saudi citizens is a key focus of the Saudi Arabian National Transformation Programme 2020 (NTP 2020) and Vision 2030 programme, which aimed to reform the country's sectors and ministries to enhance education, security, health, economics, and entertainment, which will ultimately improve the quality of life of its citizens. The international FD/MAS guidelines recommended managing FD to preserve patient QoL. Educating patients and their families was crucial to helping them understand FD and cope with complications such as bone pain, scoliosis, fractures, or immobilization. This could be achieved by establishing local and national panels of clinical experts and patient-centred social groups, which was one of the objectives of Saudi Arabia's Vision 2030. Another potential area for future research could be to examine the QoL outcomes of patients with FD/MAS in comparison to the Saudi population reference standard from all regions throughout the country. This would provide a more comprehensive understanding of our study results.

7.7 Conclusion

This study is the first to provide an assessment of the QoL and pain experienced by patients with FD/MAS in Saudi Arabia. We reported that the physical SF-36 domains scored lower than the mental domains in our study, which is supported by the literature. In addition, at follow-up, we demonstrated a strong association between the SBS (legs and pelvis) and the physical role of the SF-36 scale. The results of this study lay the groundwork for future research on the long-term impact of FD on QoL.

7.8 Reference

1. Feller, L., et al., *The nature of fibrous dysplasia.* Head & Face Medicine, 2009. **5**(1): p. 22.
2. Chapurlat, R.D. and P.J. Meunier, *Fibrous dysplasia of bone.* Best Practice & Research Clinical Rheumatology, 2000. **14**(2): p. 385-398.
3. Ricalde, P. and B.B. Horswell, *Craniofacial fibrous dysplasia of the fronto-orbital region: A case series and literature review.* Journal of Oral and Maxillofacial Surgery, 2001. **59**(2): p. 157-167.
4. Majoor, B.C.J., et al., *Pain in fibrous dysplasia: relationship with anatomical and clinical features.* Acta Orthop, 2019. **90**(4): p. 401-405.
5. Javaid, M.K., et al., *Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium.* Orphanet J Rare Dis, 2019. **14**(1): p. 139.
6. Collins, M.T., et al., *An Instrument to Measure Skeletal Burden and Predict Functional Outcome in Fibrous Dysplasia of Bone.* Journal of bone and mineral research, 2005. **20**(2): p. 219-226.
7. Kelly, M.H., et al., *Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone.* Bone, 2005. **37**(3): p. 388-94.
8. Rotman, M., et al., *Passive Coping Strategies Are Associated With More Impairment In Quality Of Life In Patients With Fibrous Dysplasia.* Calcif Tissue Int, 2018. **103**(5): p. 469-475.
9. Majoor, B.C.J., et al., *Determinants of impaired quality of life in patients with fibrous dysplasia.* Orphanet J Rare Dis, 2017. **12**(1): p. 80.
10. Hart, E.S., et al., *Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome.* J Bone Miner Res, 2007. **22**(9): p. 1468-74.
11. Stanley, F., *Reference intervals for laboratory tests and procedures.* Nelson textbook of pediatrics. 20th ed. Philadelphia: Elsevier, 2016: p. 3465t-72t.
12. Coons, S.J., et al., *Reliability of an Arabic Version of the RAND-36 Health Survey and its Equivalence to the US-English Version.* Medical Care, 1998. **36**(3): p. 428-432.
13. El Osta, N., Kanso, F., Saad, R., Khabbaz, L. R., Fakhouri, J., & El Osta, L. (2019). Validation of the SF-36 questionnaire for health-related quality of life in elderly Lebanese. *Journal of Clinical Gerontology and Geriatrics*.
14. Lins, L. and F.M. Carvalho, *SF-36 total score as a single measure of health-related quality of life: Scoping review.* SAGE Open Med, 2016. **4**: p. 2050312116671725.
15. Ballout, S., et al., *Psychometric Evaluation of the Arabic Brief Pain Inventory in a Sample of Lebanese Cancer Patients.* Journal of Pain and Symptom Management, 2011. **42**(1): p. 147-154.
16. Daut, R.L., C.S. Cleeland, and R.C. Flanery, *Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases.* Pain, 1983. **17**(2): p. 197-210.
17. Cleeland, C.S. and K.M. Ryan, *Pain assessment: global use of the Brief Pain Inventory.* Ann Acad Med Singap, 1994. **23**(2): p. 129-38.
18. Zou, K.H., K. Tuncali, and S.G. Silverman, *Correlation and simple linear regression.* Radiology, 2003. **227**(3): p. 617-22.
19. Schneider, A., G. Hommel, and M. Blettner, *Linear regression analysis: part 14 of a series on evaluation of scientific publications.* Dtsch Arztebl Int, 2010. **107**(44): p. 776-82.
20. Tsai, C.-L., Z. Cai, and X. Wu, *The examination of residual plots.* Statistica Sinica, 1998: p. 445465.
21. Mansfield, E.R. and M.D. Conerly, *Diagnostic value of residual and partial residual plots.* The American Statistician, 1987. **41**(2): p. 107-116.
22. Nesselroade, J.R., S.M. Stigler, and P.B. Baltes, *Regression toward the mean and the study of change.* Psychological Bulletin, 1980. **88**(3): p. 622-637.
23. Abdulrashid, O.A., et al., *Physical activity and health-related quality of life among adults living in Jeddah city Saudi Arabia.* PeerJ, 2023. **11**: p. e16059.
24. Konradi, A., *Fibrous dysplasia patients with and without craniofacial involvement report reduced quality of life inclusive of stigma, depression, and anxiety.* Chronic Illn, 2022. **18**(4): p. 927-936.

25. Forestier-Zhang, L., et al., *Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia.* Orphanet J Rare Dis, 2016. **11**(1): p. 160.
26. Benhamou, J., et al., *Prognostic factors from an epidemiologic evaluation of fibrous dysplasia of bone in a modern cohort: the FRANCEDYS study.* Journal of Bone and Mineral Research, 2016. **31**(12): p. 2167-2172.
27. Spencer, T.L., et al., *Neuropathic-like Pain in Fibrous Dysplasia/McCune-Albright Syndrome.* J Clin Endocrinol Metab, 2022. **107**(6): p. e2258-e2266.
28. Kelly, M.H., B. Brillante, and M.T. Collins, *Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions.* Osteoporos Int, 2008. **19**(1): p. 57-63.
29. Chapurlat, R.D., et al., *Pathophysiology and medical treatment of pain in fibrous dysplasia of bone.* Orphanet J Rare Dis, 2012. **7 Suppl 1**(Suppl 1): p. S3.
30. Bartley, E.J. and R.B. Fillingim, *Sex differences in pain: a brief review of clinical and experimental findings.* Br J Anaesth, 2013. **111**(1): p. 52-8.
31. Almalki, M.T., et al., *Prevalence of chronic pain and high-impact chronic pain in Saudi Arabia.* Saudi Med J, 2019. **40**(12): p. 1256-1266.
32. Robinson, M.E., et al., *Sex Differences in Clinical Pain: A Multisample Study.* Journal of Clinical Psychology in Medical Settings, 1998. **5**(4): p. 413-424.

Chapter 8:

Exploring the Use of the Skeletal Burden Scoring on Whole-Body MRI: Preliminary Findings from RUDY Study

8.1 Abstract

Objectives

The aim of this study was to evaluate the application of the skeletal burden score (SBS) on whole-body magnetic resonance imaging (WB-MRI) and compare it with bone scintigraphy for assessing the skeletal involvement in patients with fibrous dysplasia/McCune Albright syndrome (FD/MAS).

Methods

This retrospective study included patients enrolled in the Rare UK Disease Study (RUDY), an online registry. Patients diagnosed with FD/MAS who had bone scintigraphy and WB-MRI scans were eligible for this study. Three independent readers with different level of experience in assessing MRI scans scored all images using the SBS and compared the accessibility and usability of WB-MRI with that of bone scintigraphy. The intraclass correlation coefficient (ICC) and 95% confidence interval (CI) were calculated for all three readers to assess the reader- agreement for all scans. Descriptive analysis was performed to summarise the SBS results and reader preferences for each imaging modality.

Results

A total of 12 patients (58% female; mean age, 33.5 ± 11 years) were included. The measured SBS ranged from 0 to 39.70. Only two patients had both WB-MRI and bone scintigraphy scans available for direct comparison. Among these, bone scintigraphy was reported to be easier for evaluating FD involvement in the skull, long bones, and pelvis. The overall reader agreement was excellent, with an ICC of 0.89 (95% CI: 0.788–0.957). For bone scintigraphy, the ICC was 0.918 (95%CI: 0.792-0.972), while for WB-MRI, it was 0.85 (95%CI:0.44 - 0.972).

Conclusion

The findings indicate that the SBS can be successfully applied to WB-MRI, yielding comparable results to bone scintigraphy for the evaluation of FD skeletal involvement. Further studies involving larger cohorts are required to validate these findings.

8.2 Introduction

The role of radiological imaging in the diagnosis of fibrous dysplasia (FD) has been of interest to many researchers, owing to its diverse phenotypic variability. Bone scintigraphy, conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) were used to evaluate FD. The use of whole-body imaging to assess skeletal involvement during the diagnosis of FD is recommended by the international FD/MAS guidelines [1]. Bone scintigraphy has been widely used to assess the number of FD lesions because the radiotracer technetium 99m-methylene diphosphonate (^{99m}Tc-MDP) is taken up by the FD lesions. The uptake of the radiotracer ^{99m}Tc-MDP is not influenced by the metabolic state of the lesion or age-related changes, highlighting the unique ability of bone scintigraphy to capture the physiological state of FD involvement even in asymptomatic lesions [2, 3]. Assessing skeletal severity in such a rare disease with a wide clinical spectrum is essential for understanding and determining the disease burden of FD for each patient during diagnosis. Moreover, skeletal burden score (SBS) is the only reliable tool unaffected by age changes or the use of bisphosphonate treatment [4, 5].

Whole-body MRI (WB-MRI) is another cross-sectional imaging modality that can be used for diagnosing FD and differentiating FD lesions from other benign and malignant bone tumours [6]. The high anatomical resolution of MRI, particularly in detailed areas such as the craniofacial, maxillary and pelvic bones, is a significant advantage. Another benefit of MRI is the absence of radiation exposure, allowing repeated scans without posing any risks to the patient.

However, FD features on MRI are non-specific due to the significant influence of the amount of bone trabeculae, cysts, collagen, and cellularity present within the FD lesion [6, 7]. The appearance of FD lesions on T1- and T2-weighted MRI sequences is heterogeneous, with low to intermediate signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images [8]. Moreover, short tau inversion recovery (STIR) MRI sequence is a T1- inversion recovery technique. And designed to suppress the fat signal to zero, which enhancing the visualisation of tumours, infections, or any abnormalities within the bone marrow [9, 10]. To the best of our knowledge, the measurement of FD involvement on WB-MRI using the SBS has not yet been explored. Therefore, this study aimed to evaluate the inter-reader reliability of SBS by comparing the SBS calculated from bone scintigraphy and WB-MRI scans across three readers independently. Also, to compare the readers' perspectives on the accessibility of assessing FD involvement on WB-MRI scans versus bone scintigraphy scans.

8.3 Methods

8.3.1 Ethical approval

A local ethical approval was obtained from Oxford University Hospitals NHS Foundation Trust under (PID 12272). Patient consent was not required as the study was retrospective and involved anonymised without any patient identifiable data.

8.3.2 Study design

Retrospective analysis of 12 patients with confirmed FD/MAS who were registered in the Rare UK Diseases Study (RUDY), an online-based registry of a total 4236 participants diagnosed with rare musculoskeletal diseases. The registry includes participants' basic demographic information and completed outcome measures, such as quality of life, pain, and sleep assessments. One of registry's primary objectives is to facilitate advancement in rare disease research by providing raw data of analysis [11].

Three readers participated in this study. Two of them, referred to as Reader 1 (Professor Amaka C. Offiah, ACO) and Reader 2 (Dr Ashok Raghavan, AR), were also involved as readers in another study arm covered in **Chapters 6** and **7**. The third reader, Reader 3 (Arwa Alhulwah, AA), is a nuclear medicine technologist with 10 years of experience in the field. Reader 3 had not previously measured the SBS but possessed knowledge of its application. Notably, none of the three readers had prior experience measuring the SBS from WB-MRI scans. The MRI images were imported as DICOM files. The readers assessed T1- and T2-weighted sequences in coronal, sagittal and transverse planes. No 3D image reconstructions were performed in this study.

The inclusion criteria were as follows:

a) The patient was diagnosed with FD and registered in the RUDY registry.
b) The patient had at least one bone scintigraphy or WB-MRI scan.
c) All bone scintigraphy and WB-MRI scans were retrievable and available in the Oxford University NHS Hospital electronic system.

Patients who underwent both WB-MRI and bone scintigraphy were included in the comparative analysis of the two imaging modalities. A Likert Scale was used to assess the ease of evaluating specific skeletal compartments (skull, right and left upper extremities, right and left ribs, sternum, spine, right and left pelvis, right and left lower extremities) on WB-MRI compared to bone scintigraphy. The second part of the comparative analysis assessed the reader's preference for imaging modality and provided an opportunity for any additional comments. All readers independently scored the scans within the same one-week period.

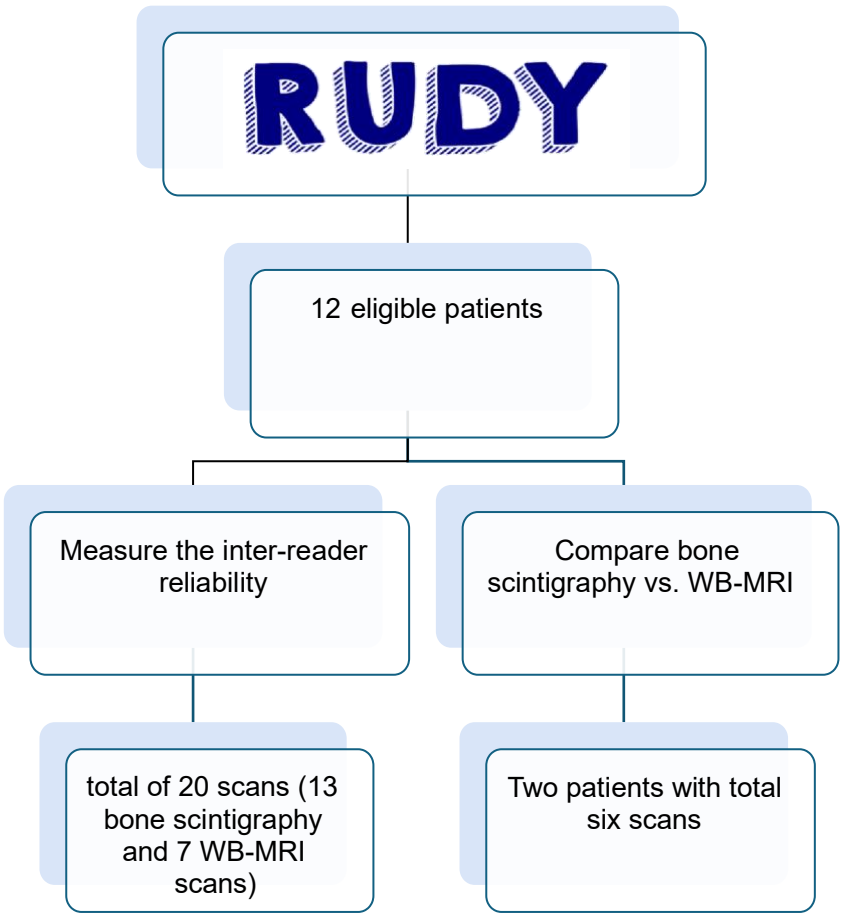


Figure 8.1 Study flowchart

8.3.3 Statistical methods

Basic descriptive statistical analysis was conducted to summarise the mean and standard deviation (SD) of the SBS, and age. Sex was reported as a number and percentage. These data were collected and presented in the study results. The measurement of reader agreement, which addresses the second aim of this study, was adapted from the statistical methodology used in Chapter 6. Reader agreement assess the variation between multiple readers assessing the same images. To calculate inter-reader agreement, intra-class correlation (ICC) was applied using two-way, mixed effects models. The ICC values were interpreted as follows: > 0.9 indicated "excellent agreement," 0.75–0.9 indicated "good agreement," 0.5–0.75 indicated "moderate agreement," and an ICC< 0.5 indicated “poor agreement” [12].

The reader’s perspectives on WB-MRI versus bone scintigraphy were assessed using a table with 11 skeletal compartments. Each reader was asked to rate the interpretability of WB-MRI compared to bone scintigraphy using Likert scale. The scale consisted of the following options: strongly disagree, disagree, neutral, agree and strongly disagree. The Likert scale is widely used for assessing of agreement, magnitude, or participants opinions. Readers were also asked to indicate their preferred image modality for assessing FD involvement in a free-text response section, allowing them to express their opinions openly. Each reader was provided with an Excel sheet pre-formulated with the SBS scoring system used in **Chapters 6** and **7**. The collected data were compiled and tabulated into figures and tables. All statistical analysis was performed using the Stata/MP 17.0 software.

8.4 Results

The basic characteristics of the included patients are summarised in Table 8.1. A total of 20 scans (bone scintigraphy and WB-MRI) from 12 patients (seven females and five males) were included in this study. The average SBS across all scans was 11.66, with a range of 0 to 39.70. The average SBS derived from bone scintigraphy was 12.09 (range: 0.05 - 38.82), while the average SBS derived from WB-MRI was 10.85 (range:0 - 39.70).

Table 8.1 Patients characteristics

Patient number	Sex	Age	FD form	History of fractures, (year)	Bone scintigraphy, (year)	WB-MRI, (year)
1	Female	31	Monostotic FD	2019	2018	-
2	Female	51	Polyostotic FD	-	-	2024
3	Male	29	FD	2016	2016	-
4	Female	24	FD	-	-	2016, 2018
5	Female	40	MAS	2009	2010	2015
6	Male	35	FD	-	2012, 2016	2018
7	Female	53	FD	-	2013	-
8	Female	59	FD		2010, 2011	-
9	Male	34	FD	2016	2014	-
10	Male	30	FD	-	2018	-
11	Male	32	FD	-	2016	2016, 2023
12	Female	52	FD	2023	2009	-

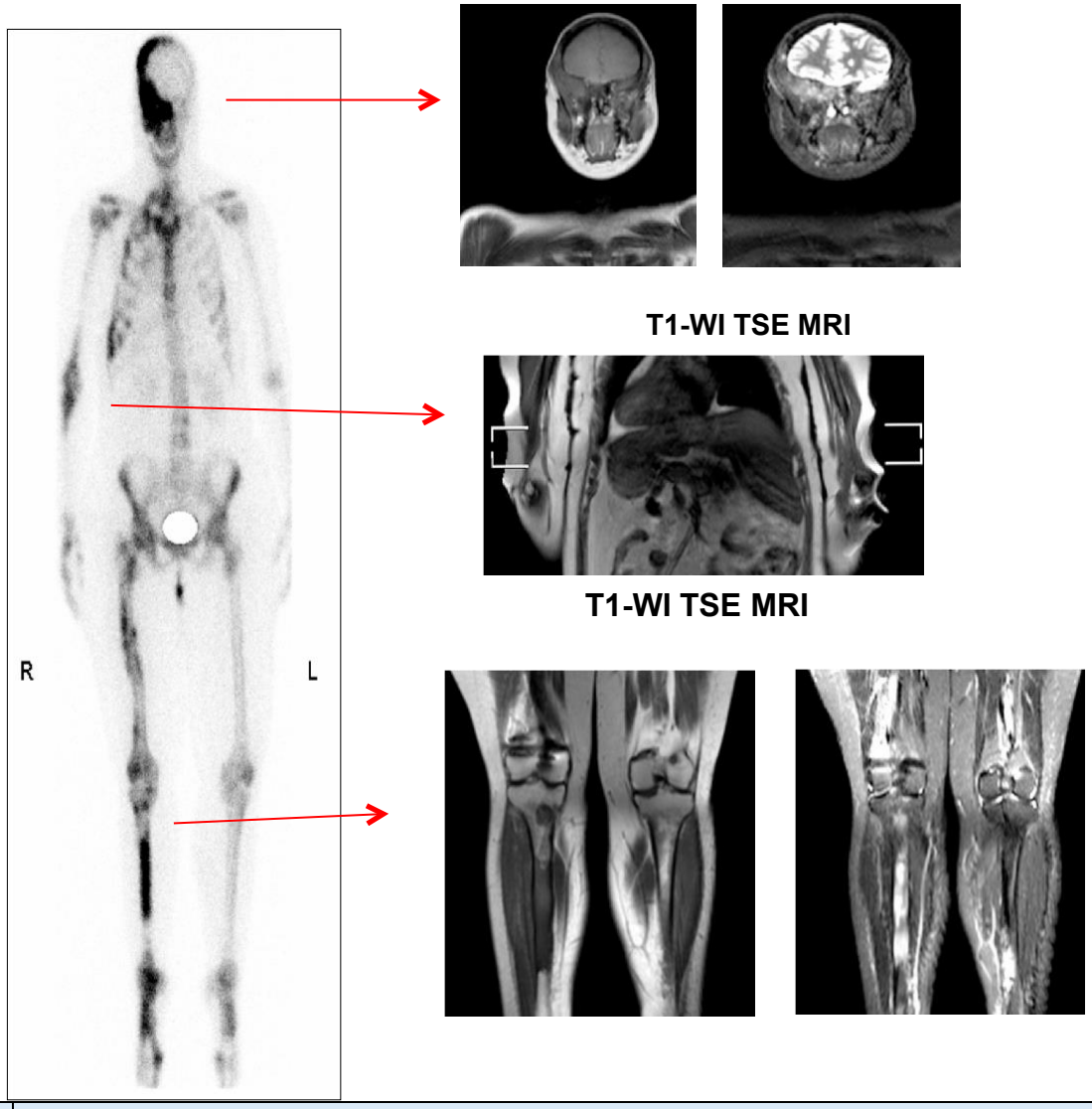
FD, fibrous dysplasia; WB-MRI, whole-body magnetic resonance imaging

8.4.1 Comparison of WB-MRI and Bone Scintigraphy in FD/MAS Patients

Only two patients (patient number 5 and 11) were eligible for the comparison of FD involvement between WB-MRI and bone scintigraphy scans. Patient # 5, a 40-year-old female patient diagnosed with MAS. The initial bone scan was done in April 2010 and was repeated in October 2010. In 2015, the patient had WB-MRI scan. All three readers reported that bone scintigraphy scans were easier than WB-MRI in the assessment of FD involvement in the skull, right and left ribs. Reader 2, and 3 also found that bone scintigraphy was easier in the assessment of other FD locations such as right and left lower extremities, and right and left pelvis. Whilst Reader 1 found that both imaging modalities are equivalent. (Fig. 2.a).

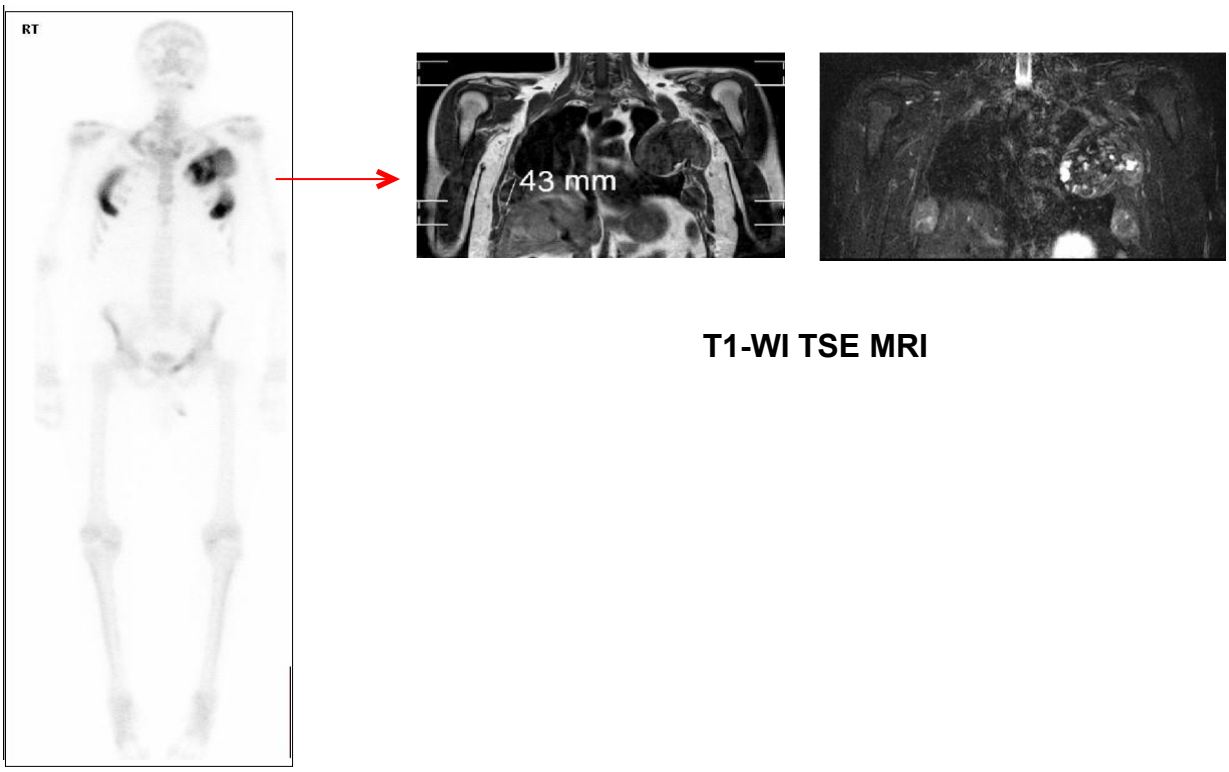
Patient #11, a 32-year-old male patient diagnosed with FD. Initial bone scintigraphy was done on June 2016 followed by WB-MRI in the same year and repeated in 2023. Reader 1 and 3, found that WB-MRI was easier to assess the FD involvement in the following compartments: right ribs, left ribs, right and left pelvis. Whilst Reader 2 thought both imaging modalities were both equal. Reader 2 and 3, found that bone scintigraphy was easier in assessing right and left upper extremities. (Fig.3.b).

a)



		Skeletal compartments										
Patient	Reader	Skull	Right Upper Extrem.	Left Upper Extrem.	Right Lower Extrem.	Left Lower Extrem.	Spine	Right ribs	Left ribs	Sternum	Right pelvis	Left pelvis
A	1	-1	0	0	0	0	0	-2	-2	-2	0	0
	2	-2	-2	-2	0	0	1	-2	-2	0	-1	-1
	3	-2	-2	-2	-1	0	-2	-2	-2	-2	-1	-1

b)



Tc-MDP bone scintigraphy

T1-WI TSE MRI

		Skeletal compartment										
Patient	Reader	Skull	Right upper Extrem.	Left upper Extrem.	Right lower Extrem.	Left lower Extrem.	Spine	Right ribs	Left ribs	Sternum	Right pelvis	Left pelvis
B	1	0	0	0	0	0	0	1	1	-2	1	1
	2	0	-1	-2	0	0	0	0	0	0	0	0
	3	1	-1	-1	1	1	0	1	1	0	1	1

Figure 8.2. The reader assessment on the easiness of assessing fibrous dysplasia (FD) involvement on whole-body magnetic resonance imaging (WB-MRI) using Five-point Likert scale.

The Likert scale scores were interpreted as following (-2 = strongly disagree, -1 = disagree, 0 =neutral, 1 = agree, 2 = strongly agree). a) patient # 1, 40 years old female diagnosed with polyostotic FD. Bone scintigraphy scan FD lesions with high ^{99m}Tc-MDP uptake. Whole-body MRI (WB-MRI) was obtained, with hypointense appearance on coronal T1-weighted Turbo spin echo (TSE) MRI imaging and hyperintense on STIR MRI sequences of the skull and lower extremities FD involvement.; b) patient # 2, 32 years old male diagnosed with polyostotic FD patient. Bone scintigraphy with abnormalities in the right and left ribs. Hypointense FD appearance on coronal, T1-weighted TSE and mixture of hypo and hyperintense with cystic appearance on STIR MRI sequences were obtained to evaluate the FD lesions. For both patients, the SBS obtained from all three readers are provided in separate tables.

8.4.2 Reliability

Overall, the inter-reader reliability was good for measuring SBS of both imaging modalities combined. The reliability of bone scintigraphy was slightly higher than WBMRI. In Table 8.2, results of the inter-reader reliability values are presented.

Table 8.2 Inter-reader reliability between the three readers in measuring SBS from bone scintigraphy and WB-MRI

Imaging modality	Number of scans	ICC	[95% CI]	p-value
Overall	20	0.90	0.78 to 0.95	<0.001
Bone scintigraphy	13	0.92	0.79 to 0.56	<0.001
WB-MRI	7	0.85	0.44 to 0.97	0.003

CI, confidence interval; ICC, intra-class correlation coefficient; WB-MRI, whole-body magnetic resonance image

8.5 Discussion

This study is the first to measure the SBS derived from WB-MRI scans, demonstrating its applicability, with good agreement among the three readers (ICC=0.90) When comparing the agreement across the two imaging modalities, bone scintigraphy showed higher ICC (0.92) compared with WB-MRI (0.85). In **Chapter 6,** we previously demonstrated that SBS showed excellent inter- and intra-reader agreement among five radiologists without prior training in SBS calculations. The findings of this study align with our previous results, further reinforcing the applicability and consistency of SBS for both bone scintigraphy and WB-MRI scans.

The radiological features of FD on MRI are known to be heterogeneous and nonspecific. However, MRI provides detailed, high-resolution images of the FD involvement and the surrounding tissues, helping to detect complications such as deformities, scoliosis, pathological fractures, and nerve compressions.

In our study, readers perceived WB-MRI to be easier for assessing large FD lesion compared to bone scintigraphy. For instance, in patient #11, all three readers stated that evaluating the FD involvement on WB-MRI specifically in the ribs was easier than bone scintigraphy. Moreover, the FD appearance on WB-MRI, in T1weighted images was an isointense signal with that of muscle, and a mixture of hypo- and hyper-intense signals on STIR sequence (Figure 2b). In patient a, the FD involvement of the pelvis, ribs, and sternum had mild ^{99m}Tc-MDP uptake on bone scintigraphy, and the readers found it difficult to assess the involvement on WB-MRI. In contrast, the FD involvement of the skull was large and demonstrated extensive uptake, as seen on bone scintigraphy. When assessing this involvement, readers found WB-MRI harder than bone scintigraphy. (Figure 2a).

Craniofacial bones are one of the most common FD locations, which has a prevalence of 10–25% in monostotic and up to 90% in polyostotic FD [13].

In a retrospective study by Kim et al. [14] evaluated MRI images of 32 patients with craniofacial FD lesions. The study involved the assessment of T1- and T2-weighted images, as well as enhanced images of the administration of Gadolinium contrast medium. Ground glass appearance was predominant in 97% of the craniofacial lesions. Also, MRI was able to differentiate FD from meningioma and identify abnormalities to the surrounded nerves and soft tissue of the brain and spinal canal.

We also noticed the presence of artifacts in the WB-MRI for patients a, and b. The artifacts were found on the upper extremities due to the placement of the arms on the abdomen during the scan. In patient a, the FD involvement of the right elbow was out of the field of view (FOV), making it difficult for readers to assess the FD involvement of the upper extremities. As a result, readers found bone scintigraphy to be simple and fast in assessing FD in such cases. In a study by Cam et al. [15], they analysed WB-MRI artifacts caused by the placement of the arm in 107 paediatric images. 26.57% artifacts were in the upper extremities, with 80% of the artifacts were in the abdomen area. Eliminating this artifact can be done by changing the position of the arms to the sides instead of the abdomen [16].

8.5.1 Limitations

This study has several limitations that may have affected the findings and the overall conclusion of the study. First, the lack of complete blinding of the readers. The scans were organised in patient-specific folders, which may have allowed readers to recognise images from the same patient across different imaging modalities. This likely introduced bias, as readers may have been subconsciously influenced by their previous knowledge of a patient's SBS when assessing subsequent scans.

Second, the sample size was relatively small, with only 12 patients included, it becomes difficult to detect meaningful statistical differences between WB-MRI and bone scintigraphy and reduced the generalisability of the findings. The impact of small sample size affected the confidence interval. WB-MRI reported (IC, between 0.44 to 0.97), indicating substantial level of variability which reduced the precision of the ICC calculations. Moreover, the comparison between WB-MRI and bone scintigraphy was based on only two patients, which is an inadequate sample size to recognise a trend or pattern or draw definite conclusions. As a result of small sample size, our findings should be regarded as preliminary and exploratory. A power calculation suggests that a minimum of 30 patients would be needed to achieve statistically robust conclusions for this study. Not all patients registered in the RUDY study had their scans performed at Oxford University Hospitals, which made obtaining completed datasets challenging.

Third, intra-reader reliability was not assessed due to time constraints during the PhD study. Only inter-reader reliability was measured, which limits the ability to evaluate the consistency of individual reader scores over time. Finally, there was a lack of complete blinding during the scoring process due to the organisation of the scans in patient-specific folders. This may have introduced bias, as readers might have been influenced by prior knowledge of SBS measurements from another scan of the same patient (all in one folder). This could lead to more consistent scoring and higher reliability values than expected. Despite these limitations, this study represents the first attempt to assess the application of SBS on WB-MRI, helping to highlight important areas for future research.

8.6 Conclusion

our preliminary study demonstrated the applicability of SBS on WB-MRI, demonstrating good reliability among three readers. These findings suggest that SBS can be applied to WB-MRI and provide comparable to those from bone scintigraphy in patients with FD/MAS. Future studies with larger, more diverse cohorts are recommended to validate these results and ensure broader applicability. Additional research should focus on optimising the SBS for WB-MRI and exploring its clinical utility in monitoring disease progression and guiding personalised management strategies.

8.7 Reference

1. Javaid, M.K., et al., *Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium.* Orphanet J Rare Dis, 2019. **14**(1): p. 139.
2. Yuan, Z.B., et al., *The role of radionuclide bone scintigraphy in fibrous dysplasia of bone.* CLINICAL NUCLEAR MEDICINE, 2004. **29**(3): p. 177-180.
3. Zhibin, Y., et al., *The Role of Radionuclide Bone Scintigraphy in Fibrous Dysplasia of Bone.* Clinical Nuclear Medicine, 2004. **29**(3): p. 177-180.
4. Collins, M.T., et al., *An Instrument to Measure Skeletal Burden and Predict Functional Outcome in Fibrous Dysplasia of Bone.* Journal of bone and mineral research, 2005. **20**(2): p. 219-226.
5. Majoor, B.C.J., et al., *Determinants of impaired quality of life in patients with fibrous dysplasia.* Orphanet J Rare Dis, 2017. **12**(1): p. 80.
6. Kushchayeva, Y.S., et al., *Fibrous dysplasia for radiologists: beyond ground glass bone matrix.* Insights Imaging, 2018. **9**(6): p. 1035-1056.
7. Shah, Z., W.C. Peh, W. Koh, and T. Shek, *Magnetic resonance imaging appearances of fibrous dysplasia.* The British journal of radiology, 2005. **78**(936): p. 1104-1115.
8. DiCaprio, M.R. and W.F. Enneking, *Fibrous dysplasia. Pathophysiology, evaluation, and treatment.* J Bone Joint Surg Am, 2005. **87**(8): p. 1848-64.
9. Tokuda, O., N. Hayashi, and N. Matsunaga, *MRI of Bone Tumors: Fast STIR Imaging as a Substitute for T1-Weighted Contrast-Enhanced Fat-Suppressed Spin-Echo Imaging.* Journal of Magnetic Resonance Imaging, 2004. **19**(4): p. 475-481.
10. Golfieri, R., H. Baddeley, J.S. Pringle, and R. Souhami, *The role of the STIR sequence in magnetic resonance imaging examination of bone tumours.* The British journal of radiology, 1990. **63**(748): p. 251-256.
11. Javaid, M., et al., *The RUDY study platform–a novel approach to patient driven research in rare musculoskeletal diseases.* Orphanet journal of rare diseases, 2016. **11**: p. 1-9.
12. *"Forming inferences about some intraclass correlations coefficients": Correction*. 1996, American Psychological Association: US. p. 390-390.
13. Kim, D.Y., *Current concepts of craniofacial fibrous dysplasia: pathophysiology and treatment.* Archives of Craniofacial Surgery, 2023. **24**(2): p. 41.
14. Kim, D., et al., *Magnetic resonance imaging features of craniofacial fibrous dysplasia.* Polish Journal of Radiology, 2019. **84**: p. e16-e24.
15. Le Cam, S., et al., *Analysis of whole-body MRI artifacts in a pediatric population with a special emphasis on the effect of hands position.* Diagnostic and Interventional Imaging, 2023. **104**(3): p. 153-159.
16. Stadler, A., et al., *Artifacts in body MR imaging: their appearance and how to eliminate them.* European radiology, 2007. **17**: p. 1242-1255.

Chapter 9:

Overall Discussion

9.1 Discussion of the thesis main findings

This study is designed with several study arms. Each study arm has its own aim and methodology. In **Chapter 3**, we systematically evaluated the relationship between skeletal burden score (SBS) and the physical health, as measured by validated health-related quality of life (HRQoL) outcome measures and ambulatory status in patients with fibrous dysplasia/McCune-Albright syndrome (FD/MAS). While a limited number of studies have used SBS as a tool to assess FD skeletal severity. Our systematic review and meta-analysis underscore the significant negative impact of FD/MAS on physical health. The systematic review concluded that SBS is reliable and unaffected by age and the use of bisphosphonate treatment for pain. Furthermore, it has been shown that SBS can predict adulthood ambulatory status in children. SBS >30 indicates a greater skeletal burden and the need for ambulatory assistive devices (crutches, canes, and in severe cases, wheelchairs).

In **Chapter 4**, we systematically assessed the diagnostic accuracy of cross-sectional imaging modalities in diagnosing FD/MAS. Magnetic resonance imaging (MR) and computed tomography (CT) were the most used modalities in the literature. Our meta-analysis demonstrated that the sensitivity and specificity of CT was superior to MRI for the diagnosis of FD/MAS and distinguishing FD from other benign and malignant bone tumours.

In **Chapter 5**, we attempted to measure the clinician's perceptions of SBS, and its use in clinical practice for diagnosing FD/MAS. We designed a short online survey for international dissemination among clinicians. Although the response rate was low, the results of the survey demonstrated limited knowledge and use of SBS among the

participants. We also highlighted potential ways to improve the survey design and questions for a future survey with the same aim.

One of the main aims of this thesis, presented in **Chapter 6**, was to evaluate the agreement between five radiologists in determining the SBS derived from technetium 99m-methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy scans of FD/MAS patients, both within and between the radiologists. Our findings demonstrated excellent intra- and inter-reader agreement across the five radiologists without prior knowledge or training in SBS. Moreover, we assessed the SBS calculated from both Digital Imaging and Communication in Medicine (DICOM) and Joint Photographic Experts Group (JPEG) image formats of bone scintigraphy scans. We found that the reliability of JPEG images was equivalent to that of DICOM images.

The second aim of this study, covered in **Chapter 7**, was to assess the relationship between SBS and the physical outcomes and bone pain at baseline and follow-up phases. We recruited FD/MAS patients from two collaborating centres in Saudi Arabia to assess the relationship between SBS and QoL and pain using a brief pain inventory (BPI). Previous studies have assessed the QoL of patients with FD/MAS from different cohorts. Saudi FD/MAS patients reported poor physical function, consistent with the literature on the impact of FD/MAS on physical abilities. Greater SBS of the lower extremities and pelvis was correlated with greater limitations in physical health. Our findings revealed that the assessment of SBS of the lower extremities and the pelvis showed a stronger correlation with role-limited due to physical health domain of SF-36 than the total SBS of all 11 compartments. Notably, this correlation was observed only in male participants, with no similar association found in females. The underlying reasons for this gender-specific finding could be further explored through a longer follow-up of the same patient cohort.

In **Chapter 8**, we expanded the use of SBS and applied it to whole-body MRI (WBMRI) scans. We collaborated with Oxford University hospitals to recruit FD/MAS patients registered in the rare UK diseases of bone joints and blood vessel (RUDY) online registry. Three readers assessed bone scintigraphy and WB-MRI images using SBS and comparing both modalities in the assessment of FD involvement. The consistency between the readers of both images was deemed to be good. However, bone scintigraphy inter-reader reliability was higher compared with WB-MRI Moreover, bone scintigraphy was found to be easier and faster than WB-MRI; however, this finding requires the assessment of a larger set of bone scintigraphy and WB-MRI scans to draw more definitive conclusion.

9.2 Strengths and Limitations

The following points highlight the key strengths of this study. First, the study design, protocol, and inclusion and exclusion criteria were developed in accordance with the recommendations provided by clinical specialists in the relevant field. Furthermore, this study was a multicentre study that included collaborating sites from the United Kingdom, such as Sheffield Children's Hospital (SCH), Northern General Hospital (NGH), and Oxford University Hospital. The King Faisal Specialist Hospital (KFSHRC) and Research Centre and King Fahad Specialist Hospital (KFSH) in Saudi Arabia the collaborating team comprise clinicians from various fields, including radiology, paediatrics, endocrinology, and orthopaedics. who demonstrated an interest in continuing to be a part of future research on FD/MAS.

Another strength of this study is the novelty of measuring the SBS from a WB-MRI scan, which is considered novel and holds potential for future SBS application in various cross-sectional imaging. However, this study is not without its limitations. The first significant limitation was the small sample size. Professor Alan Rigby calculated the required sample size to be 170 patients; however, we were only able to recruit a total of 39 patients. We encountered high rates of non-response and refusal among patients recruited from Saudi Arabia. When asked about their reasons for declining participation, approximately 13 patients cited the lack of direct benefit to themselves or their child as a primary concern. Additionally, some patients expressed a preference to be seen by a physician as a condition for participation.

Unfortunately, the existing protocol and care plan for FD/MAS in Saudi Arabia do not include regular annual follow-ups, which may have influenced the willingness of patients to participate. This limitation is related to the centre's mission, which prioritizes the diagnosis of rare diseases and the treatment of complicated cases. Bone pain was the most frequently reported complication, and treatment was generally limited to over-the-counter painkillers such as paracetamol.

Another limitation was the shortened follow-up phase. Due to the constraints of the PhD timeline, we had to reduce the duration between the baseline and follow-up phases from 12 months to 6 months. This abbreviated follow-up period may have affected the outcome measures, and as a result, medium- and long-term outcomes were not assessed. Future research could build upon our findings by extending the follow-up period to 12 months, and further studies at 5 and 10 years could provide valuable insights into the physical outcomes associated with FD/MAS.

9.3 Challenges

During the PhD programme, I faced numerous academic and personal challenges. Each challenge resulted in a positive outcome that motivated me to become a better student and researcher. In the first six months of my studies on neuroblastoma, I conducted a systematic review titled “The Diagnostic Accuracy of Whole-Body 3T-MRI Compared to ^{123}I-MIBG Nuclear Medicine Scintigraphy Scan for Detecting Skeletal Metastases in Children with Neuroblastoma” (Appendix i). The findings of the systematic review were shared with clinicians in the field, and we concluded that the study was not applicable in clinical practice and, therefore, unsuitable for a PhD programme. This led to the termination of the study. I redirected my focus and gathered my energy to read the literature to identify a knowledge gap within my field in nuclear medicine that is worth exploring. With the support of Professor Amaka C. Offiah and Dr Ashok Raghavan, I discovered a passion for learning more about the diagnostic imaging of rare diseases of such FD/MAS. After the discussions with my supervisors, we agreed on the present study.

The changes caused by the COVID-19 pandemic significantly impacted my process of obtaining ethical approval in both the United Kingdom and Saudi Arabia. This resulted in delays in patient recruitment and required multiple amendments to the recruitment protocol to comply with social distancing measures at that time. Hospital appointments were switched to phone and video calls, and many were rescheduled, which negatively affected the number of patients recruited for this study. In addition, the delay caused by COVID-19 persisted even after the restrictions were lifted, impacting the process of obtaining collaborating sites approval and access letters. For example, at Oxford University Hospital, COVID related studies were given priority over

other research studies, resulting in a delay of more than two years in starting patient recruitment.

During lockdown, I have tried to use the time to conduct the systematic review in **Chapter 3** (currently under review by *Quality-of-Life Research* journal). Also, we designed the survey study, **Chapter 6**, and disseminated it to reach broader clinicians internationally. In 2021, the sudden passing of my beloved father happened while I was in the UK with my two children. Unfortunately, I didn't get a chance to see him before the funeral due to COVID-19 restrictions. His passing affected my mental health. As a result, I took a leave of absence from my studies to be with my family in Saudi Arabia.

9.4 Future Work and Direction

Building on this study findings, future research and directions are summarised as follows:

9.4.1 Implementation of the international FD/MAS guidelines in Saudi Arabia

While working with collaborating sites in Saudi Arabia, we observed that clinicians were largely unaware of the existence of the international FD/MAS guidelines and the lack of a unified diagnosis and management plan for FD/MAS. The current diagnosis approach relies on the initial clinical complication reported, as well as the need for surgical correction or endocrine assessments. Future studies assessing clinicians' knowledge and implementation of international FD/MAS guidelines in Saudi Arabia are important. In **Chapter 6**, we propose a survey design which can be used for this purpose.

Moreover, this study established a network of specialists interested in FD/MAS related research. We plan to establish a task force focused on FD/MAS and other rare metabolic bone diseases in Saudi Arabia, with the potential to expand coverage to the Middle East. This task force will facilitate the sharing of the most up-to-date research and clinical experience in diagnosis, treatment of clinical complications and FD/MAS management. Patient- and parent-focused groups will also be part of the task force, allowing for valuable input from patients, parents and families. This input will help increase awareness of FD/MAS by creating educational materials tailored to different age groups in both Arabic and English.

9.4.2 Establishing Saudi Registry

We plan to create a Saudi online registry platform comprising of participants diagnosed with FD/MAS. The registry includes demographic data, disease history, and validated outcome measures such as QoL and pain. The Saudi registry will assist clinicians in better understanding the disease, encourage researchers to engage in relevant studies, and help patients and their families to connect with specialists who can address their concerns and questions. This registry will aid in conducting a longitudinal observational study of the QoL of patients with FD/MAS in Saudi Arabia, aligning with the new Saudi Arabia Vision 2030 goals for economic, social, and health reforms. One of the main goals of 2030 is to improve the overall quality of life, specifically the QoL of patients, and deliver optimal patient care.

9.4.3 Advancing SBS

To reduce overscoring SBS of specific compartments, specifically the lower extremities compartment, which was noticed in Chapter 6. To minimise reader's confusion, we suggest further division of SBS of the lower extremities into two compartments. Furthermore, the femur, which is one of the most common sites of FD involvement, is currently considered part of the lower extremities. However, we have observed that readers sometimes confuse femur involvement with the pelvis area. Therefore, we propose dividing the SBS of the lower extremities into specific compartments: the femur, tibia, and fibula. Additionally, with the emergence of artificial intelligence (AI), deep learning techniques can be employed to create automated scoring systems for calculating SBS. Training deep learning models, such as convolutional neural networks (CNNs), to calculate SBS from cross-sectional image data could significantly enhance accuracy and efficiency.

9.5 Conclusion

In conclusion, this study underscores the use of SBS in assessing skeletal severity and physical outcomes. The SBS demonstrated excellent intra- and inter-reader agreement calculated from bone scintigraphy. And SBS demonstrated good inter-reader reliability calculated from whole-body MRI. These findings support the potential for integrated SBS into clinical practice, and further research is encouraged to explore its implementations.

Chapter 10 :

Appendices and references

Appendix I. Health Research Authority Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Prof Amaka Offiah
Chair of Paediatric Musculoskeletal Imaging and
Honorary Consultant Paediatric Radiologist
The University of Sheffield
University of Sheffield , Academic Unit of Child Health ,
Damer Street Building , Western Bank
Sheffield
S10 2THN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

29 July 2021

Dear Professor Offiah

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The Use of the Skeletal Burden Score (SBS) for Predicting Outcomes in Children and Adults with Fibrous Dysplasia**
IRAS project ID:	**277033**
Protocol number:	**N/A**
REC reference:	**21/EM/0094**
Sponsor	**Sheffield Children's Hospital**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

Appendix II. Sheffield Children's Hospital Letter of Access

Sheffield Teaching Hospitals NHS
NHS Foundation Trust
Research Department

Letter of access for researchers who do not require an honorary research contract

1 March 2022

Arwa Alhulwah
Metabolic Bone Centre
Northern General Hospital
Herries Road
Sheffield
S5 7AU

Dear Arwa

STH ref: 22070
Study title: The Use of the Skeletal Burden Score (SBS) for Predicting Outcomes in Children and Adults with Fibrous Dysplasia
Chief Investigator: Amaka Offiah **Principal Investigator:** Jennifer Walsh

Letter of access for research
This letter confirms your right of access to conduct research through Sheffield Teaching Hospitals NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on **1 March 2022** and ends on **29 September 2022** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permissionconfirmation from the individual organisation(s) of their agreement to conduct the research.

The information supplied about your role in research at Sheffield Teaching Hospitals NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

Status
You are considered to be a legal visitor to Sheffield Teaching Hospitals NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

Reporting Arrangements
While undertaking research through Sheffield Teaching Hospitals NHS Foundation Trust you will remain accountable to your substantive employer/place of study **University of Sheffield** but you are required to follow the reasonable instructions of **Jennifer Walsh** in this NHS organisation or those instructions given on their behalf in relation to the terms of this right of access.

Legal Claims
Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

Policies and Procedures
You must act in accordance with Sheffield Teaching Hospitals NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

Appendix III. Collaborating site – KFSH Ethical Approval

Institutional Review Board (IRB)
National Registration Number (H-05-D002)
Tel: +966 13 8443333, Ext: 2978, 2903
Email: IRB@kfsh.med.sa

Research Center
King Khalid Medical City (RC-KKMC)
King Fahad Specialist Hospital-Dammam

وزارة الصحة
Ministry of Health

APPROVAL OF PROTOCOL

This letter is issued to replace IRB approval letter issued on 01/11/2021, the special determination part is added

09 December 2021

Emad Al-Absi
Consultant Orthopedic and Musculoskeletal Oncology Surgeon
King Fahad Specialist Hospital-Dammam
emad.absi@kfsh.med.sa

Dear Dr. Al-Absi,
On *04 October 2021,* the IRB reviewed the following protocol:

IRB Study Number	ORTH0001			
Title	The Use of the Skeletal Burden Score (SBS) for Predicting Outcomes in Children and Adults with Fibrous Dysplasia			
Principle Investigator	Emad Al-Absi			
Sub-Investigator(s)	1. Arwa Alhulwah. 2. Omar Salem. 3. Fouad Al-Adel.			
Sponsor	The ministry of higher education			
Type of Submission	Initial submission			
Level of Review	Full Board			
IRB Review Outcome	Approved			
Special determinations	1. Permission of one parent is sufficient even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. 2. Assent to be documented as follow: the submitted parent/Adult ICF has a check box to document the assent and there are assent forms for different age groups that will be used in the assent process.			
Effective Date **Expiry Date** **Documents Reviewed** **Documents Reviewed**	01/11/2021 31/10/2022 **Document Type**	**Document Title**	**Document Version #**	**Document Date**
	Protocol and related documents	Institutional Review Board Protocol Template	3.0	20/09/2021
		Sheffield Children's Foundation Trust- Imaging Protocol Bone scan	Bone v1.2	-
		Whole-Body MRI Protocol	1.0	20/09/2021
	CRF	CRF Skeletal Disease Burden Score Calculator	1.0*	September 2021*
		Clinical data collection sheet	1.0*	01/11/2021*

Appendix IV. Bone Scintigraphy scanning protocols

SHEFFIELD CHILDREN'S HOSPITAL

Date	Version	Comments	Written By	Approved By	Next Review
Nov 2013	1.0	Initial issue	M Haines	P Broadley	Nov 2015
Nov 2015	1.1	Routine review	M Haines	P Broadley	Nov 2017
Dec 2017	1.2	Routine review	M Haines	P Broadley	Dec 2019

Bone Scan

Valid Reason for Examination

- **Primary or secondary bone tumours**
- **Osteomyelitis**
- **Assessment of fractures/healing/non-union**
- **Avascular Necrosis**

Comments	
Radiopharmaceutical	99mTc HDP
Preparation	• *Weigh and record patient weight and check patients' id. • *Apply EMLA (in patients over the age of 1 year) 1 hour before the injection. • *Patients under 6 months of age to be cannulated on Medical Daycare. • Note any recent fractures or injuries on the request card
Dose	• Max 600MBq , Min 60MBq • Patient dose is calculated by measuring the patient weight and calculating the fraction of adult dose using the paediatric radiopharmaceutical spreadsheet (available in the Isotope room and protocol book).
Time Scale	• Injection given IV 2-4 hours prior to scan
Collimator	• Low Energy High Resolution
Protocol	• SCH Bone
Images	• Patient in supine position • Position feet first <u>Whole body</u> • from vertex to toes with arms by side (use arm support). • Scanner H Mode • Matrix – 1024*256 • Zoom 1 • 99mTc window • Anterior and Posterior • Speed 8cm/min • Read the patient start/end positions from the

	bed markings and enter into the start/end positions on the console. Statics • As required/requested • Scanner H Mode • Matrix – 256*256 • Zoom 1 • 99mTc window • Time 300 seconds per acquistion SPECT • Area as directed by Consultant Radiologist • Scanner H Mode • Matrix – 128*128 • Zoom 1 • 99mTc window • Time 10 seconds per projection • $2*360^0$ rotation • 3^0 per rotation
Technique	• Select correct patient from modality worklist • Set up acquisition as per worklist protocol • Acquire all required images as described above. • Consultant Radiologist to review images before patient leaves department.
Aftercare	• Post injection if - the child is wearing a nappy, give parents gloves and bag to store them and give advice re handwashing. Nappy bags should be collected when patient returns for scan and labelled and stored. In older children, give advice re handwashing and flushing the toilet. • Restrictions apply until the injected dose has decayed to below 400 MBq. This can be calculated using the spreadsheet which is found on the computer at G:\RADIOLOG.PAE\RADIOLOG\ISOTOPES\ISOTOPES\HOTLAB\Tc99m decay calculator.xls • Advise parents/carers of the time that radioactivity is below 400 MBq and hand them the advice sheet. See G:\RADIOLOG.PAE\RADIOLOG\ISOPTOPES\ISOTOPES\HOTLAB\Tc99m restrictions letterv1.xls
Processing/Display/PACS	• Use the Whole Body Review Template on Xeleris to produce screen captures and send to PACS • Use the Load to New Function to produce screen captures for any static images and send to PACS. • Use the Tomo Oblique Slicing function to

	produce Axial, Coronal and Sagittal SPECT images, create screenshots and then send to PACS • Send original images to LOUIE • Send all images and captures to CACHE

BONE SCINTIGRAPHY:

Primary Indications:	To evaluate for skeletal metastases, metabolic disease, infection, hematologic or trauma.
Interfering Conditions:	(1) Diphosphonate therapy. Treatment for hypercalcemia with diphosphonate compounds blocks the skeletal uptake of Tc-99m diphosphonates, and bone scintigraphy may not give satisfactory results until several weeks after discontinuation of the medication (2) Prior scintigraphy (or therapy) with other radionuclides (especially I-131, Ga-67, or In-111) (3) Barium administration. The radio-opaque barium may obscure skeletal structures.
Precautions	None.
Radiopharmaceutical:	Preferentially Tc-99m methylene diphosphonate (MDP). If Tc-99m MDP is unavailable thanTc-99m hydroxymethylene diphosphonate (HDP) is an acceptable substitute.
Adult Dose:	25 mCi (20-40 mCi)
Pediatric Dose:	250 μCi/kg with a minimum dose of 2.5 mCi
Radiation Dosimetry:	Adult. Critical organ (bladder): 3 rem. Effective dose: 0.6 rem. Infant (1-year=2.5 mCi). Critical organ (bladder): 1.5 rem. Effective dose: 0.38 rem.
Route of Administration:	Intravenous, usually with injection in an antecubital fossa vein. **Note:** If there is suspected pathology at the elbow or in one upper extremity (typically in a patient being evaluated for wrist pain), injection should be made in the contralateral upper extremity.
Patient Preparation:	Technologist will explain the procedure and answer all the necessary questions by the patient. NM physician can be consulted if needed. Pregnancy and breast feeding status of all females of child bearing age must be determined prior radioactive injection. The patient should be well hydrated prior to and during the study. Ask the patient to drink more fluids after the radiopharmaceutical IV Injection. The Patient should empty the urinary bladder prior to the scan.

Note: Patients who cannot urinate should be catheterized.

Equipment Setup:

Gamma camera: Large field of view with SPECT/CT capabilities
Collimator: Low energy, high resolution, parallel hole (for SPECT).
Pinhole collimator may be useful particularly in children.
Energy window: 20% window centered at 140 keV.

Examination Time:

Total procedures time: 5 hours
Preparation and injection: 30 minutes
Delay time 2-3 hours (HDP) 3-4 hours (MDP)
Scan Time: 1-2 hours (Including SPECT CT if needed)

ACQUISITION PROTOCOL:

Area of interest is to be determined by NM Physician or resident or as vetted on request form

Dynamic: Ant/Post (or as determined by Attending Physician), 30 frames at 2sec/frame with 64x64 matrix

Static (Blood Pool): Ant/Post (or as determined by Attending Physician) with 256x256 matrix and 300 sec with zoom as required at 5 minutes

Delayed Spots (after 2-4 hours): Ant/Post Spots of the Pelvis post void and Ant/Post spot of the chest with arms up all for 700k counts each or 5 minutes whichever comes first. Right and left anterior obliques of skulls for 400k counts or 5 minutes whichever comes first.

Limited Bone scan might be requested with spot views only and no WBS: Appropriateness of additional spot views or SPECT/CT is to be determined by the NM Physician. Area of interest to be determined by the NM physician.

Delayed WBS (after 2-4 hours): Ant/Post WBS with a scan speed of 10cm/min.
Have the patient empty his/her bladder immediately before image acquisition.

Bone SPECT and SPECT/CT: Area of interest to be determined by NM physician.

SPECT CT: See SPECT CT procedure guidelines

DATA PROCESSING:

DYNAMIC, SPOTS AND WB

Appendix IV. Collaborating site- KFSHRC confirmation of Ethical

University of Sheffield

Arwa Alhulwah <aalhulwah1@sheffield.ac.uk>

FW: Research Application The Use of the Skeletal Burden Score SBS for Predicting Outcomes in Children and Adults with Fibrous Dysplasia. by ALSUGAIR, ABDULAZIZ has been approved

3 messages

ALSUGAIR, ABDULAZIZ SALEH <asugair@kfshrc.edu.sa> 5 December 2021 at 11:15
To: Arwa Alhulwah <aalhulwah1@sheffield.ac.uk>

From: converis-support@kfshrc.edu.sa [mailto:converis-support@kfshrc.edu.sa]
Sent: Sunday, December 05, 2021 10:38 AM
To: ALSUGAIR, ABDULAZIZ SALEH <asugair@kfshrc.edu.sa>
Subject: Research Application The Use of the Skeletal Burden Score SBS for Predicting Outcomes in Children and Adults with Fibrous Dysplasia. by ALSUGAIR, ABDULAZIZ has been approved

Dear ALSUGAIR ABDULAZIZ,

Congratulations! Your research application titled The Use of the Skeletal Burden Score (SBS) for Predicting Outcomes in Children and Adults with Fibrous Dysplasia. has been approved.

The Research Ethics Committee (REC)'s other comments or suggestions are:

As above

As above

The Research Ethics Committee (REC)'s Memo to Pi is:

Date: 12 October 2021
Subject: RAC# 2211203 Ethical Concern for New Proposal
The above - referenced Research proposal reviewed by the Research Ethics Committee on 11 October 2021.
The Committee recommended Conditionally Approve the proposal provide the Following Forms are upload as soon as possible:-

1. Certificate of Assent of Minor "Arabic & English version"
2. Revised the Informed Consent Form based on the attached reviewer's comments

Please Uplode your reply/ Assent and revsied Infomed Consent From as soon as possible but not later than 12 November 2021.
Thank you.
As above

You can access the Research application here.
When prompted to login to the system, please use your ID and password that you use to access your computer on a daily basis (e.g. User name: F54346).

For help and questions please contact us on converis-support@kfshrc.edu.sa or call 44202.

Thank you,
The Office of Research Affairs

Appendix V. Adult Patient Information Sheet

INSERT TRUST/INSTITUTION LOGO

PARTICIPANT INFORMATION SHEET FOR ADULTS

Study title: The Use of the Skeletal Burden Score (SBS) for Predicting Outcomes in Children and Adults with Fibrous Dysplasia

You are being invited to take part in a research study. This study is part of (Mrs Arwa Alhulwah) educational qualifications. The information gathered in this study will be used in her final assessment for (PhD) qualification from the University of Sheffield. The Chief Investigator for this study is Prof Amaka C Offiah, at the University of Sheffield and Sheffield Children's NHS Foundation Trust.

Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others about the study if you wish.

Part 1 - tells you the purpose of this study and what will happen if you decide to take part.

Part 2 - gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 - To give you first thoughts about the study

1. What is the purpose of the study?

We are interested in understanding more about fibrous dysplasia (FD) disease. So, we are doing a large study using a computer-based quantitative analysis tool called (SBS) which stands for "Skeletal Burden Score". This validated analysis tool is designed to measure the severity of the skeletal burden in patients with fibrous dysplasia, which means it measures how bad fibrous dysplasia is affecting the patient's health. The SBS is calculated by applying it to whole-body medical images. Based on your treating physician's preference, the medical imaging can be either whole-body MRI scans or nuclear medicine bone scans.

In this study, we will ask you to fill in Quality of Life (QoL), pain assessment questionnaires, now and again after one year. We will use the answers from the questionnaires to compare them with the calculated SBS score to evaluate the SBS abilities to predict future physical abilities to perform daily activities. We are hoping that this study will help doctors understand the impact of fibrous dysplasia on the patient's quality of life.

INSERT TRUST/INSTITUTION LOGO

2. Why have I been invited?

You are invited because you have been diagnosed with fibrous dysplasia. Fibrous dysplasia is a condition where healthy bones are replaced by abnormal fibrous tissue lesion or multiple lesions in the skeletal system. Fibrous dysplasia may cause bone pain, breakage of the bones, a curvature of the back, abnormal bone shapes and other problems. Not all individuals with fibrous dysplasia experience the same symptoms. Some individuals have no symptoms and diagnosed accidentally during an investigation for an unrelated medical problem. In total, we aim to recruit 170 children and adults from hospitals around the UK and Saudi Arabia.

3. Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep, and we will ask you to sign a consent form. If you choose to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

4. What will happen to me if I decide to take part?

If you decide to take part, during your routine hospital visit you will be asked the following:

- To sign a written consent form and will be given a copy of this information sheet for you to keep.
- We will use the medical images that you have ever had to calculate (SBS). If your treating doctor orders a new nuclear medicine bone scan or whole-body MRI scan as part of your standard care, we will also use these images to calculate (SBS). No additional scanning is required for this research.
- Also, we will collect basic information from your hospital notes such as (race, sex, age, history of fractures and medications) this information will help the study.
- We will ask you to fill in two questionnaires during your visit today and again after 12 months, either during your clinical appointments or online based on your preference. Completing the questionnaires will not take more than 15 minutes.

5. What do I have to do?

There are no restrictions or requirements for this study. All we ask you to do is to fill in two short questionnaires, no additional scans or testing is required for this research purposes. We are aiming to make your involvement as simple and flexible as possible.

6. What are the possible disadvantages and risks of taking part?

There are no additional risks associated with taking part. Nuclear medicine bone scan and/or whole-body MRI are part of your routine care. If you take part in this study, you will not undergo any additional radiological imaging. For the nuclear medicine bone scan, we use ionising radiation to form images of your body which provides your doctor with other clinical information. This scan delivers low radiation from the radiotracer. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chances of this happening to you the same whether you take part in this study or not, because you will be having the nuclear medicine bone scan to help with your treatment and not because of this study. Whole-body MRI scans, use a magnetic field and radio waves to produce images of your body. There is no radiation risk associated with whole-body MRI scans.

7. What are the possible benefits of taking part?

While there are no direct benefits to you from taking part in this study, we hope that the data gained will help us establish better diagnostic and disease monitoring techniques for fibrous dysplasia.

8. What will happen when the research stops?

We will collect all the information together and we will decide if it is useful in telling us if the doctors can manage fibrous dysplasia better in the future.

9. What if there is a problem?

We do not anticipate any problems. However, any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on this is given in Part 2

10. Will my taking part in this study be kept confidential?

Yes, we will follow required ethical and legal practice, and all information about you will be handled in confidence. Details are included in Part 2

Contact for further information

If you would like any further information about this study, you can contact the Chief Investigator:
Prof. Amaka C. Offiah
Chair in Paediatric Musculoskeletal Radiology & Honorary Consultant Radiologist
Sheffield Children's Hospital
Tell: 0114 271 7557

This completes Part 1 of the information sheet.

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If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2 – more detailed information you need to know if you still want to take part.

11. What happens if I do not want to carry on with the research?

You may withdraw from the study at any time if you wish. But we will use the anonymised data collected up to the point of your withdrawal.

12. What if there is a problem?

Complaints

If you have any cause to complain about any aspect of the way in which you have been approached or treated during this study, you should contact:

The study Chief Investigator:

Name: Prof. Amaka Offiah
Telephone: 0114 271 7557
Email: a.offiah@sheffield.ac.uk

If you remain unhappy and wish to complain formally, you can do this by contacting:

Patient Advice & Liaison Services (PALS)
Sheffield Children's NHS Foundation Trust
Tel: 0114 271 7594
Email: scn-tr.pals@nhs.net

Harm

In the event that something does go wrong, and you are harmed during the research and this is due to someone's negligence, then you may have grounds for legal action for compensation, but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

13. Will my taking part in this study be kept confidential?

All information collected about you during this research will be kept strictly confidential. All original Identifiable data such as the consent forms will be kept in a locked cabinet in a locked office within a locked department at Sheffield's Children Hospital for 6-12 months after the completion of the study. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Once the study is complete, all anonymised information gathered will be kept and placed on a password protected electronic database held on an NHS password-protected computer for five years and then destroyed. Our procedures for handling, processing, storage, and destruction of data are compliant with the Data Protection Act 1998.

Responsible members of the Sheffield Children's Hospitals NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with the applicable regulations.
Other people who work at the hospital may also look at your medical notes to check that the study is being carried out correctly.
Other researchers may wish to access data from this study in the future. However, it will not be possible to identify you from this data because it will not include any identifiable data such as names, addresses, or date of birth. In case the anonymised data is used for future studies, REC approval will be required, and the chief investigator (Prof. Amaka C. Offiah) will ensure that the other researchers comply with legal data protection and ethical guidelines. Access to the study database will be password protected and will be used only by named researchers working in the study under the direct supervision of the chief investigator.

14. What will happen to any samples I give?

No samples will be collected.

15. Will any genetic tests be done?

No genetic tests will be performed.

16. What will happen to the results of the research study?

When the study has finished, we will present our findings to other doctors, and we will put the results in medical magazines and websites and/or presented at conferences. If the results of the study are published, your identity will remain confidential. The anonymous results will also be included as part of the PhD student's (Mrs Arwa Alhulwah) educational qualification.

17. Who is organising and funding the research?

The research is being organised and sponsored by Sheffield Children's NHS Foundation Trust. Princess Nourah Bint Abdul Rahman University, Saudi Arabia and the Royal Embassy of Saudi Arabia Cultural Bureau are funding the project.

18. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This study was given a favourable ethical opinion for
conduct in the NHS by East Midlands- Leicester South Research Ethics Committee. It has also been approved by the Sheffield Children's NHS Foundation Trust.

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General Data Protection Regulation Information

Sheffield Children's NHS Foundation Trust is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Sheffield Children's NHS Foundation Trust will keep identifiable information about you for 5 years after the study has finished, in some instances personal data maybe kept for longer where there is explicit consent in place.

You can find out more about how we use your information at the following link:
https://www.sheffieldchildrens.nhs.uk/your-information/
Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

Sheffield Children's NHS Foundation Trust will use your name, hospital number and other identifiers to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. The only people at Sheffield Children's NHS Foundation Trust who will have access to information that identifies you will be people who need to contact you regarding your participation in the study, or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, or contact details.

The following website provides information about how your information is used in research: https://www.hra.nhs.uk/information-about-patients/
Your information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.
If you would like to find out more information regarding research at Sheffield Children's NHS Foundation Trust, then please follow the link:
https://www.sheffieldchildrens.nhs.uk/research/

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If you decide to take part in this study, you will be given this information sheet and signed the consent form to keep.

Thank you for taking the time to read this information sheet.

Appendix VI. KFSH Patient Information Sheet

دعوة للمشاركة بدراسة بحثية

عنوان البحث: استخدام درجة التحمل الهيكلي (SBS) للتنبؤ بالنتائج لدى الأطفال والبالغين المصابين بخلل التنسج الليفي

الباحث الرئيسي: د.عماد العيسي

نود أن نطلعك على دراسة بحثية نقوم بها. الدراسات البحثية هي الوسيلة لمعرفة المزيد عن أي شيء. نود معرفة المزيد عن موضوع تأثير مرض خلل التنسج الليفي على النتائج الوظيفية وعلاقاته بألم العظام. أنت مدعوا/ة للانضمام الى هذه الدراسة لأنه تم تشخيصك بمرض خلل التنسج الليفي.

إذا وافقت على المشاركة بهذه الدراسة، سوف يطلب منك توقيع نموذج موافقة خطية تسمح لنا بموجبها الاستعانة بصورك الطبية لتحليل شدة الهيكل العظمي وذلك باستخدام أداة تحليل كمي حاسوبي تسمى درجة التحمل الهيكلي (SBS). فقد تخضع لفحوصات طبية إضافية مثل التصوير بالرنين المغناطيسي لكامل الجسم و / أو فحص العظام بالطب النووي. في فحص العظام بالطب النووي، يستخدم الإشعاع المؤين لتكوين صور لجسمك والتي تزود الطبيب بالمعلومات السريرية. على الرغم من أن الفحص يعتبر ذو إشعاع منخفض إلا أن الإشعاع المؤين يمكن أن يتسبب في تلف الخلايا الذي قد يتحول بعد سنوات عديدة إلى سرطان لا سمح الله. في فحوصات التصوير بالرنين المغناطيسي لكامل الجسم، استخدام المجال المغناطيسي وموجات الراديو لإنتاج صور لجسمك. لا توجد مخاطر إشعاعية مرتبطة فحص التصوير بالرنين المغناطيسي لكامل الجسم, لكن قد يطلب طبيبك تخدير عام أثناء التصوير بالرنين المغناطيسي, وهذا قد يسبب حساسية عند بعض المرضى. طبيبك سيتأكد من عدم حدوث أي مضاعفات قبل التخدير.

بعد ذلك سوف نطلب منك ملء استبيان مرتين الى 3 مرات خلال مدة البحث (الآن بعد 6 أشهر وبعد 12 شهراً) وذلك لقياس جودة الحياة والأخرى لقياس مستوى الألم. أيضاً سنستخرج المعلومات الطبية ذات الصلة من سجلاتك في المستشفى.

أخيرًا، سوف نربط جميع البيانات ببعضها. بالرغم من أننا لا نتوقع أن تحدث لك أية مخاطر أو أضرار خلال هذه الدراسة، إلا أنه في حال شعرت أن أي جزء من هذه الدراسة قد أثّر سلبًا عليك، يرجى التواصل مع د. عماد العيسي , استشاري جراحة العظام في مستشفى الملك فهد التخصصي.

لا يمكننا أن نعدك بأي فائدة شخصية لقاء مشاركتك في هذه الدراسة، إلا أننا نأمل أن تساعدنا البيانات المكتسبة في ابتكار تقنيات جديدة لتشخيص ومتابعة مرض خلل التنسج الليفي متابعةً أفضل.

ليس عليك الانضمام إلى هذه الدراسة. الأمر متروك لك. يمكنك أن توافق الآن وتغير رأيك لاحقا. كل ما عليك القيام به هو أن تقول لنا أنك تريد التوقف. لن يعتب أي شخص إن كنت لا تريد المشاركة في الدراسة أو إذا شاركت بالدراسة وغيرت رأيك في وقت لاحق وتوقفت.

قرارك بالمشاركة أو لا, لن يؤثر على وضعك العلاجي أو الوظيفي أو الدراسي

قبل أن تقول نعم أو لا للمشاركة هذه الدراسة، فإننا سنرد على أية أسئلة لديك. إذا اشتركت بالدراسة، يمكنك طرح الأسئلة في أي وقت. كل ما عليك قوله للباحث أنه لديك سؤال.

إذا كان لديك أي أسئلة حول هذه الدراسة لا تتردد في الاتصال:

د. عماد العيسي (استشاري جراحة العظام)
البريد الالكتروني: Emad.absi@KFSH.med.sa
رقم الجوال # 054255476

إذا قمت بتعبئة الاستبانة أدناه، فهذا يعني أنك توافق على المشاركة في هذه الدراسة البحثية.

لقد روجعت هذه الدراسة واعتُمدت من قِبل لجنة أخلاقيات البحث بمستشفى الملك فهد التخصصي بالدمام، وفقاً للوائح المعمول بها في المملكة العربية السعودية و التي تهدف إلى حماية حقوق مصلحة المشاركين في البحث. ويُمكنك التحدث إليهم عبر الهاتف: +966-1 3-844 2978 أو +966-1 3-844 2905 أو البريد الإلكتروني: IRB@kfsh.med.sa بخصوص أيّ مما يلي:

- أسئلتك، ومخاوفك، أو شكواك التي لم تتم إجابتك عنها من قِبل فريق الدراسة.
- لا يُمكنك الوصول لفريق الدراسة.
- ترغب في التحدث إلى شخص ما إلى جانب فريق الدراسة.
- لديك أسئلة حول حقوقك كمشارك في الدراسة.

Appendix VII. KFSHRC Patient Information Sheet

Patient's Nameplate

مستشفى الملك فيصل التخصصي ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

Title of Proposal:

The Use of the Skeletal Burden Score (SBS) for Predicting Outcomes in Children and Adults with Fibrous Dysplasia

Part I – Research Participant Information Sheet:

A. Purpose of the Research:

You are invited to participate in this scientific research because you / your child has been diagnosed with fibrous dysplasia. Fibrous dysplasia is a condition where healthy bones are replaced by abnormal fibrous tissue. Fibrous dysplasia may cause bone pain, breakage of the bones, a curvature of the back, abnormal bone shapes and other problems. Some individuals have no symptoms and are diagnosed accidentally during an investigation for an unrelated medical problem.

B. Description of the Research:

We are interested in understanding more about fibrous dysplasia. So, we are doing this research using a computer-based quantitative analysis tool called (SBS) which stands for "Skeletal Burden Score". This validated analysis tool is designed to measure the severity of the skeletal burden in patients with fibrous dysplasia (FD), which means it measures how bad FD is affecting the patient's health. The SBS is calculated by applying it to whole-body medical images. Based on your treating physician's preference, the scans can be either whole-body MRI scans or nuclear medicine bone scans. In this study, we will ask you to fill out Quality of Life (QoL), pain assessment questionnaires, now, after 6 months and again after one year. The completion of the

عنوان البحث:

استخدام درجة التحمل الهيكلي (SBS) للتنبؤ بالنتائج لدى الأطفال والبالغين المصابين بخلل التنسج الليفي

الجزء الأول – معلومات للمشارك في البحث

أ. الغرض من البحث:

انت مدعو للمشاركة في دراسة بحثية،لأنك قد شخصت /شخص طفلك بخلل التنسج الليفي. خلل التنسج الليفي هو حالة تستبدل فيها العظام السليمة بأنسجة ليفية غير طبيعية. قد يسبب خلل التنسج الليفي الألم وكسور في العظام و انحناء في الظهر وبسبب أشكال عظام غير طبيعية و غيرها من المشاكل. قد لا تظهر أي أعراض على بعض الأشخاص ولكن يتم تشخيصهم صدفة أثناء فحوصات مشكلة طبية مختلفة تماما.

ب. وصف البحث:

إننا نرغب بمعرفة المزيد عن خلل التنسج الليفي. لذلك، سنستخدم خلال هذا البحث أداة تحليل كمي باستخدام الحاسب الآلي تسمى (SBS) والتي تعني "درجة التحمل الهيكلي". تم تصميم أداة التحليل المعتمدة هذه بحيث تقيس شدة التحمل الهيكلي لدى المرضى المصابين بخلل التنسج الليفي (FD)، أي أنه يقيس مدى تأثير خلل التنسج الليفي على صحة المرضى. يتم حساب درجة التحمل الهيكلي SBS من خلال تطبيقه على الصور الطبية لكامل الجسم. بناء على تفضيل طبيبك المعالج، فإن إجراء الفحوصات يكون إما تصوير بالرنين المغناطيسي MRI لكامل الجسم، أو التصوير النووي للعظام. سنطلب منك /من طفلك في هذه الدراسة ملء استبانات جودة الحياة (QoL) واستبانات تقييم الألم بين الحين، بعد 6 أشهر والأخر بعد عام واحد . لن يستغرق الإجابة على الاستبيانات أكثر من 15

For ORA Official Use Only
INFORMED CONSENT FOR RESEARCH WITH NO DIRECT BENEFITS TO PARTICIPANT
This Consent Document is Approved for use by the Research Ethics Committee of KFSH&RC

ORA A C

(ORA 5.1.5.2) 23Oct 2000

From: 24 November 2021
To: 24 November 2022
RAC# : 2211203

إقرار بالموافقة على بحث
بدون فائدة مباشرة للمشاركين

Appendix VIII. KFSHRC Assent Form

المجلس الاستشاري للأبحاث

شهادة موافقة قاصر

عنوان البحث:

استخدام درجة التحمل الهيكلي(SBS) للتنبؤ بالنتائج لدى الأطفال والبالغين المصابين بخلل التنسج الليفي

رقم البحث:

اشهد بأن الدكتور/ ---------- قد أوضح بالكامل لـ ---------- وجود ولي أمره(طبيعة هذا البحث و الفوائد المرجوة منه والأخطار المحتملة عن المشاركة فيه بأسلوب سهل وبلغة بسيطة يتمكن الطفل من فهمها. كما أشهد بموجب هذا الإقرار بأن الطفل قد أعطى فرصة كاملة للسؤال عن مشاركته في البحث وقد تم إخباره بأن المشاركة في البحث تطوعية وليست إجبارية وان بامكانه الانسحاب حين يشاء. كما أفهم بان الطفل أعطى موافقته الشفوية للمشاركة في هذا البحث بدون إكراه. وأشهد بأنه لا توجد أي علاقة شخصية بيني وبين الطفل أو بيني وبين مشروع البحث الذي يطالب الطفل بالمشاركة فيه.

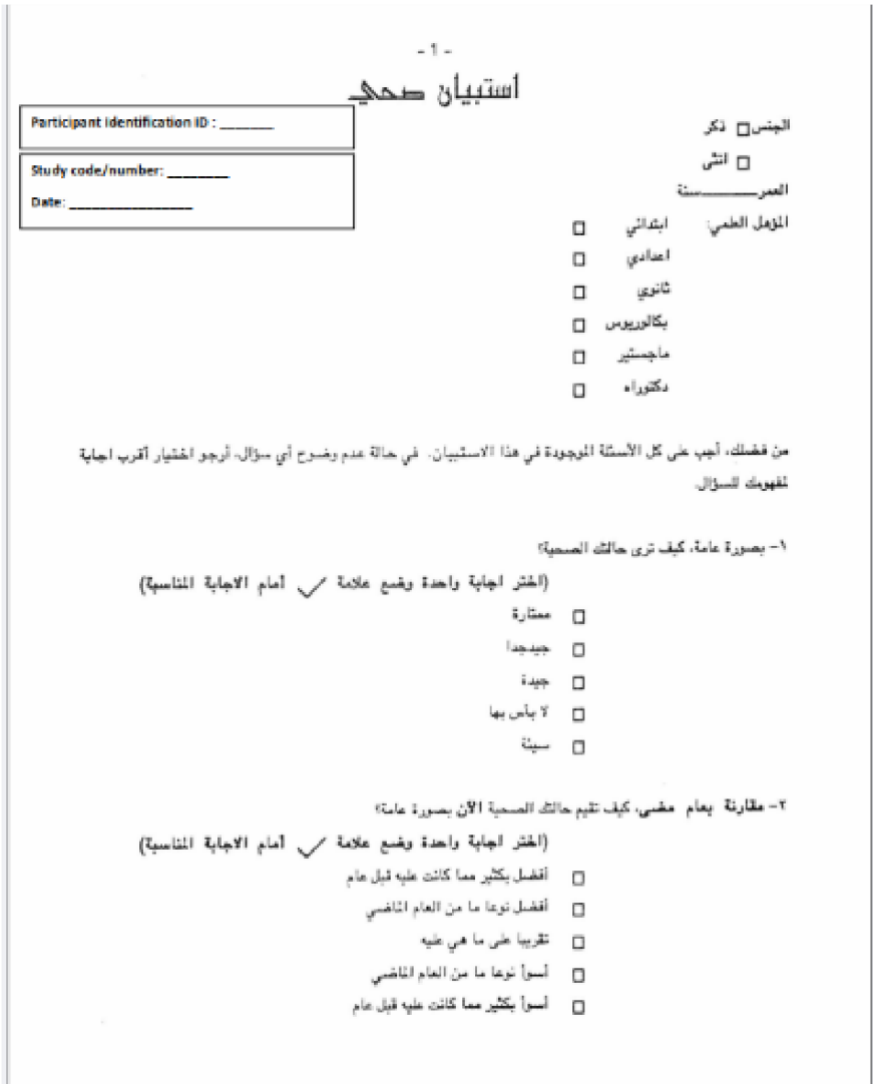
اسم الشاهد:

التوقيع:

التاريخ:

OBA
A
C

Appendix IX.SF-36 Arabic version



- 1 -

استبيان صحي

Participant identification ID : _____

Study code/number: _____

Date: _____

الجنس ☐ ذكر

☐ انثى

العمر _____ سنة

المؤهل العلمي: ☐ ابتدائي

☐ اعدادي

☐ ثانوي

☐ بكالوريوس

☐ ماجستير

☐ دكتوراه

من فضلك، أجب على كل الأسئلة الموجودة في هذا الاستبيان. في حالة عدم وضوح أي سؤال، أرجو اختيار أقرب اجابة لمفهومك للسؤال.

١- بصورة عامة، كيف ترى حالتك الصحية؟

(اختر اجابة واحدة وضع علامة ✓ أمام الاجابة المناسبة)

☐ ممتازة

☐ جيدجدا

☐ جيدة

☐ لا بأس بها

☐ سيئة

٢- مقارنة بعام مضى، كيف تقيم حالتك الصحية الآن بصورة عامة؟

(اختر اجابة واحدة وضع علامة ✓ أمام الاجابة المناسبة)

☐ أفضل بكثير مما كانت عليه قبل عام

☐ أفضل نوعا ما من العام الماضي

☐ تقريبا على ما هي عليه

☐ أسوأ نوعا ما من العام الماضي

☐ أسوأ بكثير مما كانت عليه قبل عام

٣- تتعلق البنود التالية بأنشطة يمكن ان تقوم بها خلال يومك العادي. **في الوقت الحالي**، الى اي مدى تقيدك حالتك الصحية:	(اختر اجابة واحدة وضع علامة ✓ تحت الاجابة المناسبة)		
	نعم تقيدني كثيرا	نعم تقيدني قليلا	لا تقيدني اطلاقا
أ) من ممارسة **الأنشطة الشاقة** مثل: الجري، حمل الاشياء الثقيلة او مزاولة الأنشطة الرياضية المجهدة جدا؟	☐	☐	☐
ب) من ممارسة **الأنشطة متوسطة الجهد**، كتحريك الطاولة او التنظيف باستخدام المكنسة الكهربائية او تنظيف حديقة المنزل والعناية بها ؟	☐	☐	☐
ج) من حمل المشتريات من البقالة او السوق المركزي (السوبرماركت)؟	☐	☐	☐
د) من صعود الدرج **لعدة ادوار**؟	☐	☐	☐
هـ) من صعود الدرج **لدور واحد فقط**؟	☐	☐	☐
و) من الانحناء او الركوع او السجود ؟	☐	☐	☐
ز) من المشي **لأكثر من كيلومتر ونصف**؟	☐	☐	☐
ح) من المشي **لمسافة نصف كيلومتر**؟	☐	☐	☐
ط) من المشي **لمسافة مئة متر**؟	☐	☐	☐
ي) من الاستحمام او ارتداء الملابس بنفسك؟	☐	☐	☐

الصحة الجسمية

٤- تتعلق البنود التالية (أ ، ب ، ج ، د) بالمشاكل التي يمكن ان تواجهك خلال تأديتك لعملك او للأنشطة اليومية المعتادة نتيجة لحالتك الصحية الجسمية. **خلال الأسابيع الأربعة الماضية**، هل تسببت حالتك الصحية الجسدية في: (اختر اجابة واحدة وضع علامة ✓ تحت الاجابة المناسبة)	نعم	لا
أ) **التقليل من الوقت** الذي تقضيه في العمل او اي انشطة اخرى؟	☐	☐
ب) **التقليل** مما تود **انجازه** من العمل أو اي أنشطة أخرى؟	☐	☐
ج) **تقييدك في** أداء **نوع** معين من الأعمال أو أي أنشطة أخرى؟	☐	☐
د) **أن تجد صعوبة في** تأدية العمل أو أي أنشطة أخرى؟ (على سبيل المثال، احتجت الى جهد اضافي لتأديتها)	☐	☐

الصحة النفسية

٥- تتعلق البنود التالية (أ ، ب ، ج) بالمشاكل التي يمكن ان تواجهك خلال تأديتك لعملك او الانشطة اليومية المعتادة كنتيجة لحالتك الصحية النفسية. (مثلا الشعور بالاكتئاب او القلق) **خلال الاسابيع الأربعة الماضية**، هل تسببت حالتك الصحية النفسية في: (اختر اجابة واحدة وضع علامة ✓ تحت الاجابة المناسبة)	نعم	لا
أ) **التقليل من الوقت** الذي تقضيه في العمل او اي انشطة اخرى؟	☐	☐
ب) **التقليل** مما تود **انجازه** من العمل أو اي أنشطة أخرى؟	☐	☐
ج) **عدم انجاز** العمل او اي انشطة اخرى **بالحرص المعتاد**؟	☐	☐

الصحة الجسمية او النفسية

٦- خلال الاسابيع الاربعة الماضية، الى اي مدى تعارضت صحتك الجسمية او النفسية مع تأديتك لنشاطاتك الاجتماعية المعتادة مع عائلتك او اصدقائك او جيرانك او اي من المناسبات الاجتماعية الأخرى؟

(اختر اجابة واحدة وضع علامة ✓ أمام الاجابة المناسبة)

- ☐ لم يكن هناك أي تعارض اطلاقا
- ☐ كان هناك تعارض قليل
- ☐ كان هناك تعارض متوسط
- ☐ كان هناك تعارض كبير
- ☐ كان هناك تعارض كبير جدا

شدة الألم

٧- ما شدة **الألم الجسمي** الذي عانيت منه خلال الاسابيع الاربعة الماضية؟

(اختر اجابة واحدة وضع علامة ✓ أمام الاجابة المناسبة)

- ☐ لم يكن هناك أي ألم
- ☐ كان هناك ألم خفيف جدا
- ☐ كان هناك ألم خفيف
- ☐ كان هناك ألم متوسط
- ☐ كان هناك ألم شديد
- ☐ كان هناك ألم شديد جدا

٨- خلال الاسابيع الاربعة الماضية، الى اي مدى ادى الالم الجسمي الى التعارض مع تاديتك لاعمالك المعتادة (سواء داخل المنزل او خارجه)؟

(اختر اجابة واحدة وضع علامة ✓ أمام الاجابة المناسبة)

- ☐ لم يكن هناك أي تعارض
- ☐ كان هناك تعارض قليل جدا
- ☐ كان هناك تعارض متوسط
- ☐ كان هناك تعارض كبير
- ☐ كان هناك تعارض كبير جدا

٩- الأسئلة التالية تتعلق بكيفية شعورك وطبيعة سير الأمور معك **خلال الأسابيع الأربعة الماضية**. الرجاء اعطاء اجابة واحدة لكل سؤال بحيث تكون هذه الاجابة هي الأقرب الى الحالة التي كنت تشعر بها.

خلال الأسابيع الأربعة الماضية، كم من الوقت:

(اختر اجابة واحدة وضع علامة ✓ تحت الاجابة المناسبة)

	طوال الوقت	في معظم الوقت	في كثير من الوقت	في بعض الوقت	في قليل من الوقت	لم اشعر في أي وقت من الاوقات
أ) شعرت بأنك مليء بالحيوية والنشاط؟	☐	☐	☐	☐	☐	☐
ب) كنت شخصا عصبيا جدا؟	☐	☐	☐	☐	☐	☐
ج) شعرت بأنك في حالة اكتئاب الى درجة لم يمكن معها ادخال السرور اليك؟	☐	☐	☐	☐	☐	☐
د) شعرت بالهدوء والطمأنينة؟	☐	☐	☐	☐	☐	☐
هـ) كانت لديك طاقة كبيرة؟	☐	☐	☐	☐	☐	☐
و) شعرت بالاحباط واليأس؟	☐	☐	☐	☐	☐	☐
ز) شعرت بأنك منهك (استُنْفِذت قُواك)؟	☐	☐	☐	☐	☐	☐
ح) شعرت بأنك شخص سعيد؟	☐	☐	☐	☐	☐	☐
ط) شعرت بأنك تعيس؟	☐	☐	☐	☐	☐	☐

١٠- **خلال الاسابيع الأربعة الماضية**، ما مقدار الوقت الذي تعارضت فيه **صحتك الجسمية** او **مشاكلك النفسية** مع نشاطاتك الاجتماعية (مثل زيارة الأصدقاء والاقارب وغير ذلك) ؟

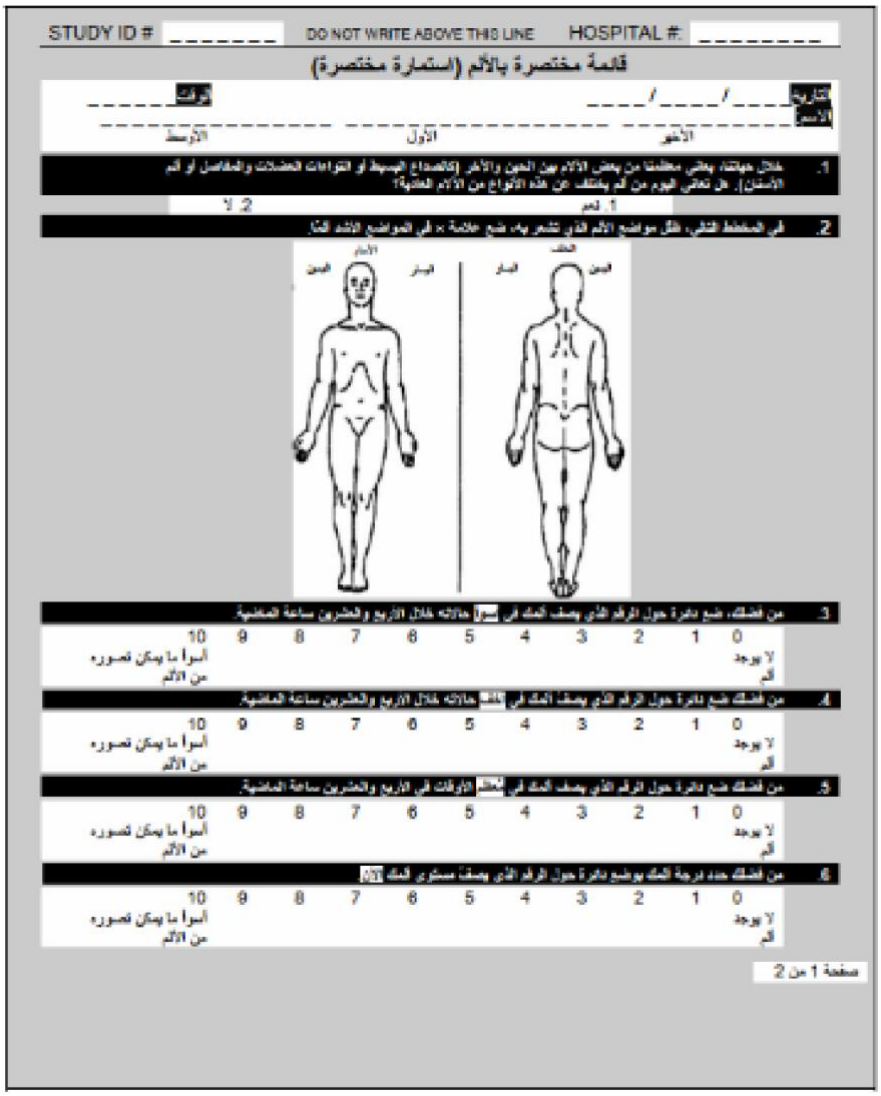
(اختر اجابة واحدة وضع علامة ✓ أمام الاجابة المناسبة)

- ☐ كان التعارض في كل الأوقات
- ☐ كان التعارض في معظم الأوقات
- ☐ كان التعارض في بعض الأوقات
- ☐ كان التعارض في قليل من الأوقات
- ☐ لم يكن هناك تعارض في أي وقت من الأوقات

١١- ما مدى **صحة او خطأ كل** من العبارات التالية (أ ، ب ، ج ، د) بالنسبة الى حالتك الصحية؟	(اختر اجابة واحدة وضع علامة ✓ امام الاجابة المناسبة)				
	صحيحة بلا شك	صحيحة غالبا	لا اعلم	خطأ غالبا	خطأ بلا شك
أ) يبدو أنني أصاب بالمرض أسهل من الآخرين.	☐	☐	☐	☐	☐
ب) حالتي الصحية مساوية لأي شخص أعرفه.	☐	☐	☐	☐	☐
ج) أتوقع أن تسوء حالتي الصحية.	☐	☐	☐	☐	☐
د) حالتي الصحية ممتازة.	☐	☐	☐	☐	☐

****** شكرا لتعاونكم ******

Appendix X. BPI Arabic version



STUDY ID # _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

قائمة مختصرة بالألم (استمارة مختصرة)

التاريخ _____/_____/_____ الوقت _____

الاسم: الأخير _____ الأول _____ الأوسط _____

1. خلال حياتك، هل عانيت من بعض الآلام بين الحين والآخر (كالصداع البسيط أو التوترات العضلات والمفاصل أو آلام الأسنان)؟ هل تعاني اليوم من ألم يختلف عن هذه الأنواع من الآلام العادية؟

1 نعم 2 لا

2. في المخطط التالي، ظلل مواضع الألم الذي تشعر به، ضع علامة x في المواضع الأشد ألماً.

3. من فضلك، ضع دائرة حول الرقم الذي يصف ألمك في أسوأ حالاته خلال الأربع والعشرين ساعة الماضية.

0 لا يوجد ألم — 1 2 3 4 5 6 7 8 9 10 أسوأ ما يمكن تصوره من الألم

4. من فضلك ضع دائرة حول الرقم الذي يصف ألمك في أقل حالاته خلال الأربع والعشرين ساعة الماضية.

0 لا يوجد ألم — 1 2 3 4 5 6 7 8 9 10 أسوأ ما يمكن تصوره من الألم

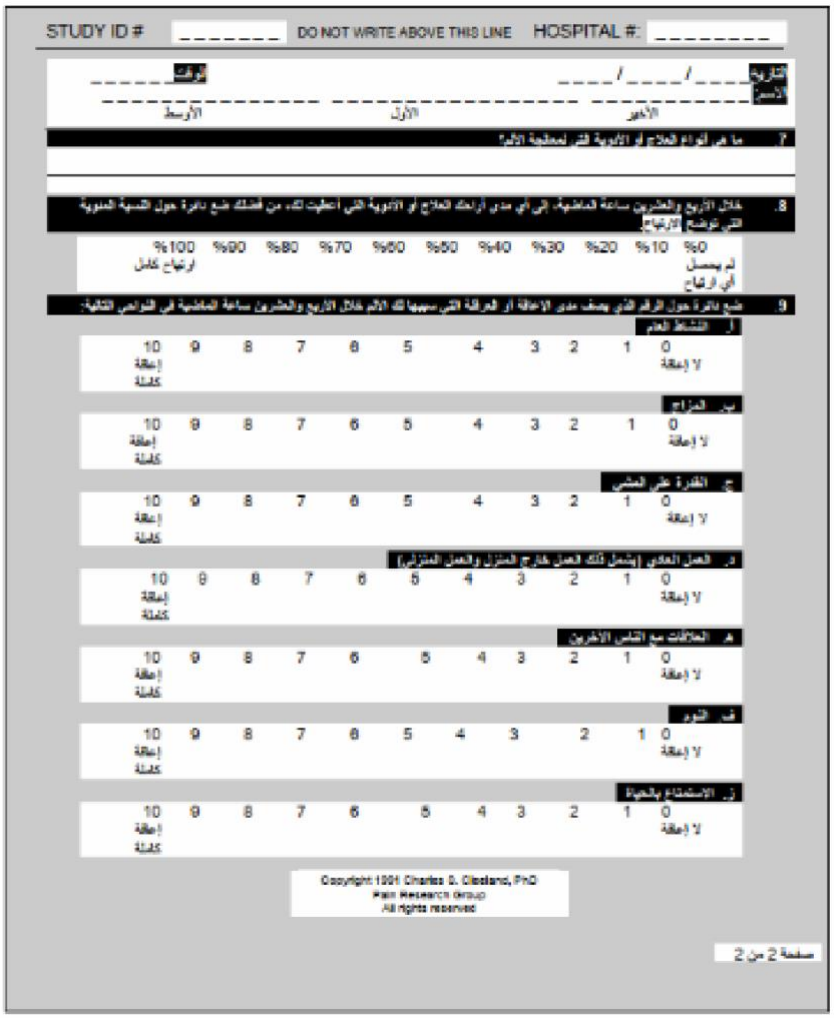
5. من فضلك ضع دائرة حول الرقم الذي يصف ألمك في المعتاد الأوقات في الأربع والعشرين ساعة الماضية.

0 لا يوجد ألم — 1 2 3 4 5 6 7 8 9 10 أسوأ ما يمكن تصوره من الألم

6. من فضلك حدد درجة ألمك بوضع دائرة حول الرقم الذي يصف مستوى ألمك الآن.

0 لا يوجد ألم — 1 2 3 4 5 6 7 8 9 10 أسوأ ما يمكن تصوره من الألم

صفحة 1 من 2



STUDY ID # _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

التاريخ ____/____/____ الوقت _____

الاسم _____ _____ _____

الأخير الأول الأوسط

7. ما هو أنواء العلاج أو الأدوية التي تعالجها الآن؟

8. خلال الأربع والعشرين ساعة الماضية، إلى أي مدى أزالك العلاج أو الأدوية التي أعطيت لك، من فضلك ضع دائرة حول النسبة المئوية التي توضح الارتياح

0% لم يحصل أي ارتياح | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% ارتياح كامل

9. ضع دائرة حول الرقم الذي يصف مدى الإعاقة أو العرقلة التي سببها لك الألم خلال الأربع والعشرين ساعة الماضية في النواحي التالية:

أ. النشاط العام

0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

ب. المزاج

0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

ج. القدرة على المشي

0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

د. العمل العادي (يشمل ذلك العمل خارج المنزل والعمل المنزلي)

0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

هـ. العلاقات مع الناس الآخرين

0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

ف. النوم

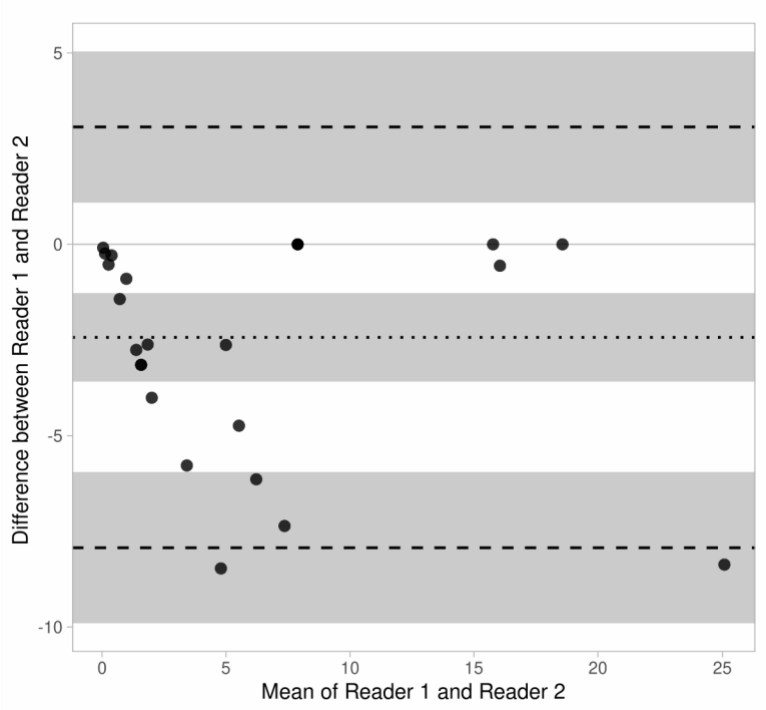
0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

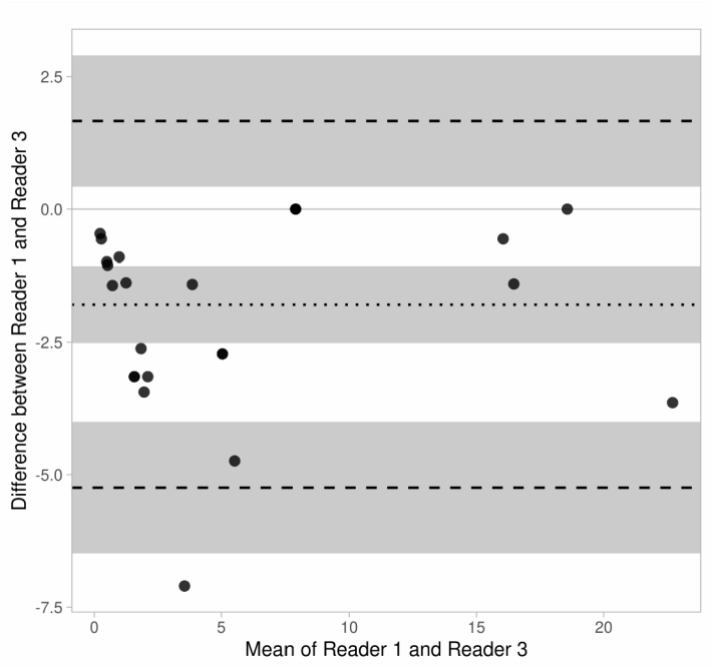
ز. الاستمتاع بالحياة

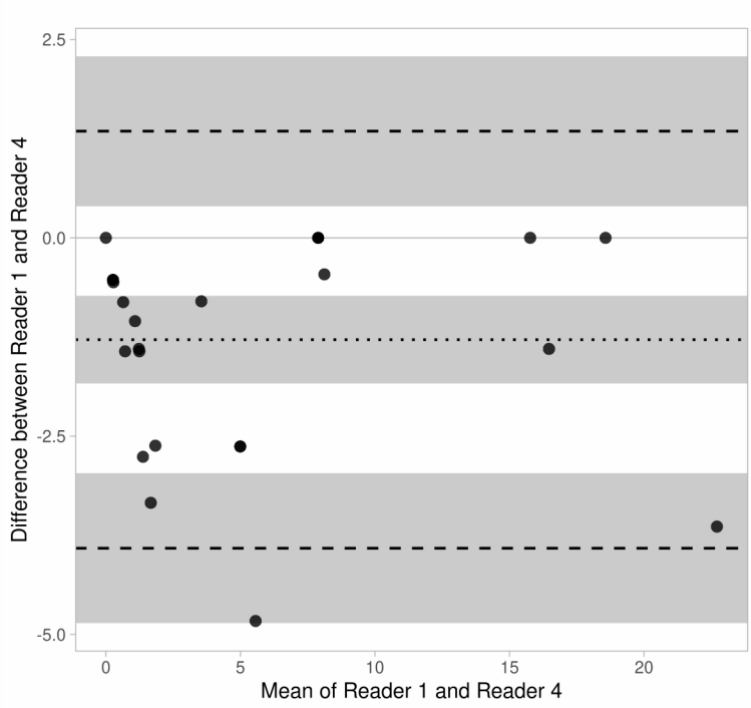
0 لا إعاقة | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 إعاقة كاملة

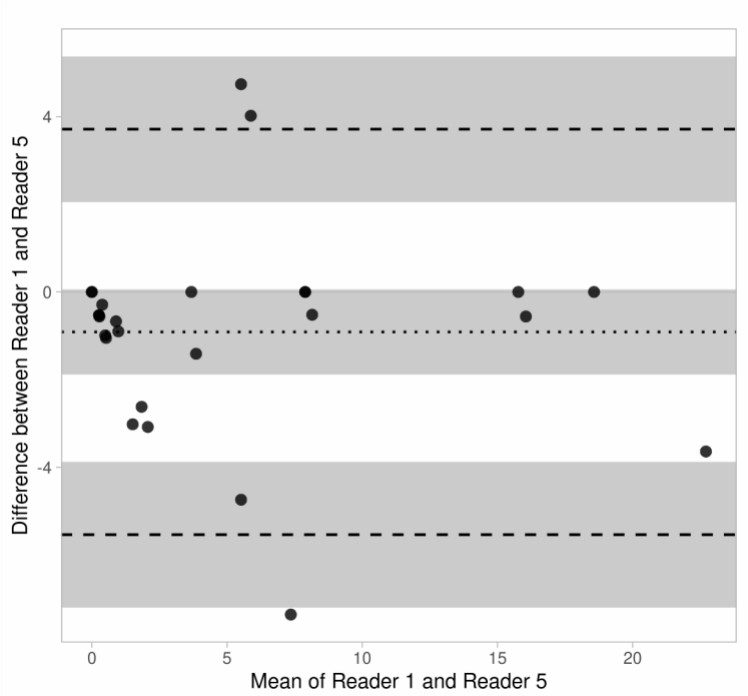
صفحة 2 من 2

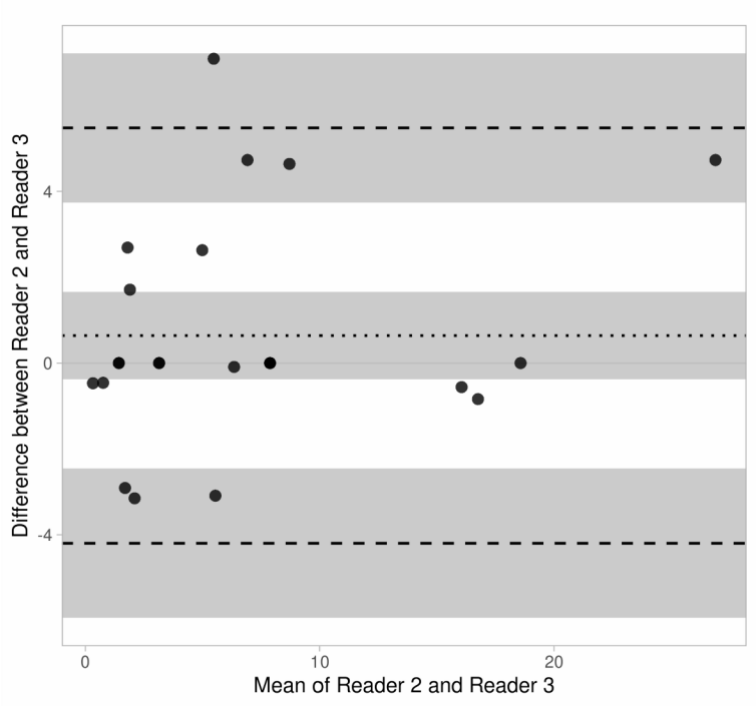
Appendix XI. Inter-reader Agreement Bland-Altman Plots

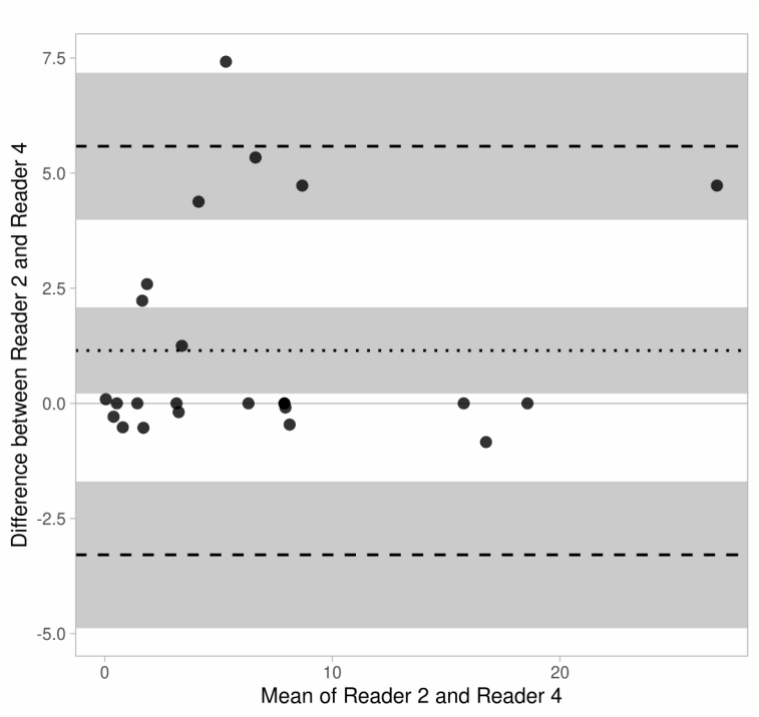


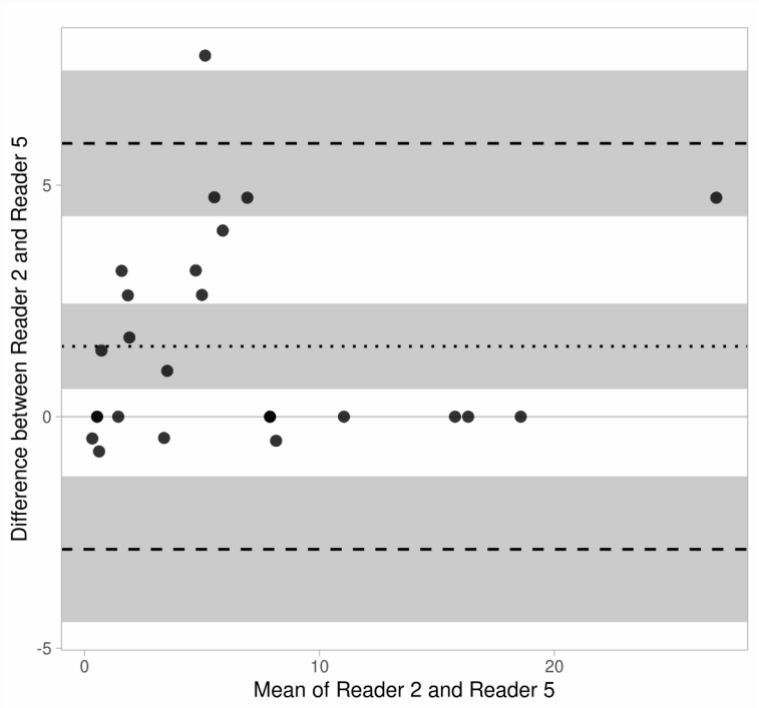

Difference between Reader 1 and Reader 3
2.5
0.0
-2.5
-5.0
-7.5
0
5
10
15
20
Mean of Reader 1 and Reader 3

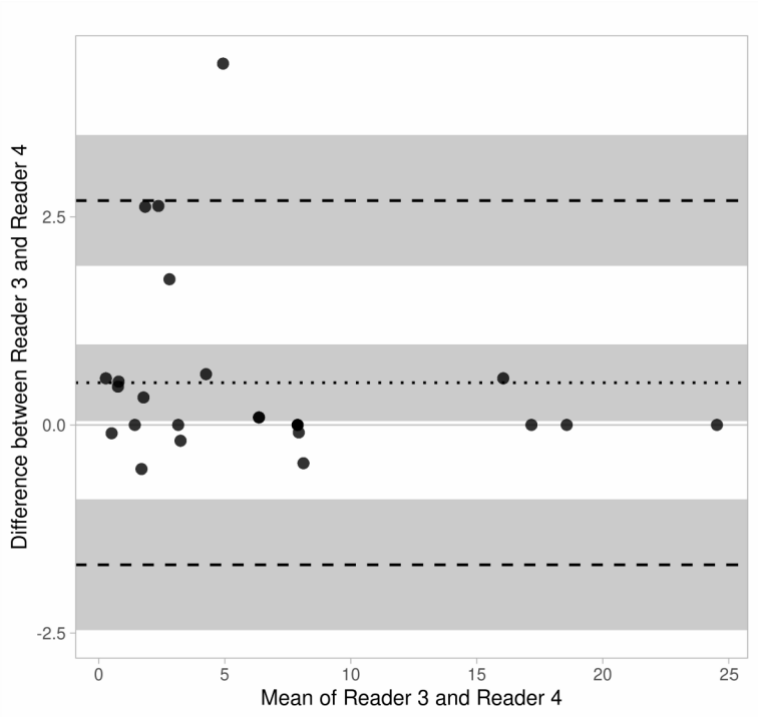

Difference between Reader 1 and Reader 4
2.5
0.0
-2.5
-5.0
0
5
10
15
20
Mean of Reader 1 and Reader 4

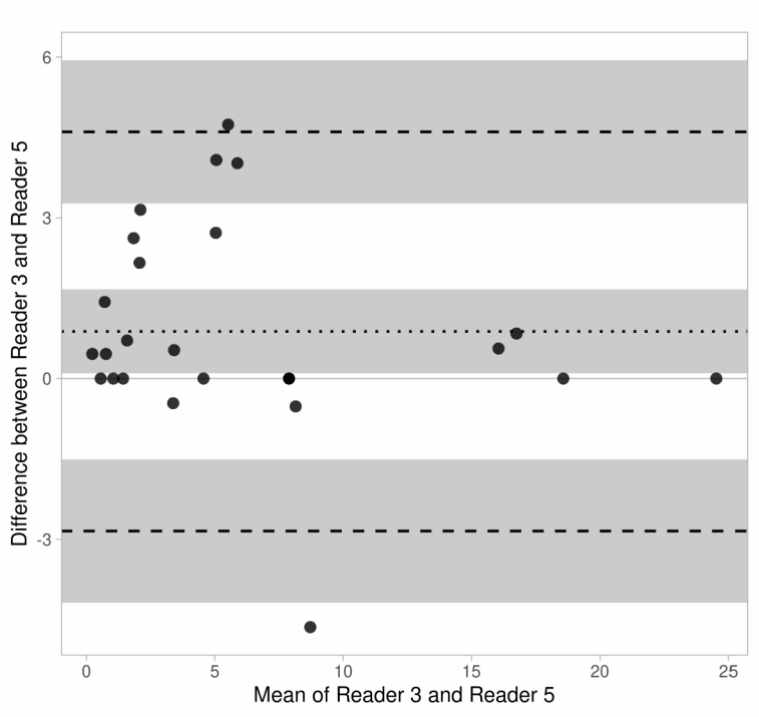

Difference between Reader 1 and Reader 5
4
0
-4
0
5
10
15
20
Mean of Reader 1 and Reader 5

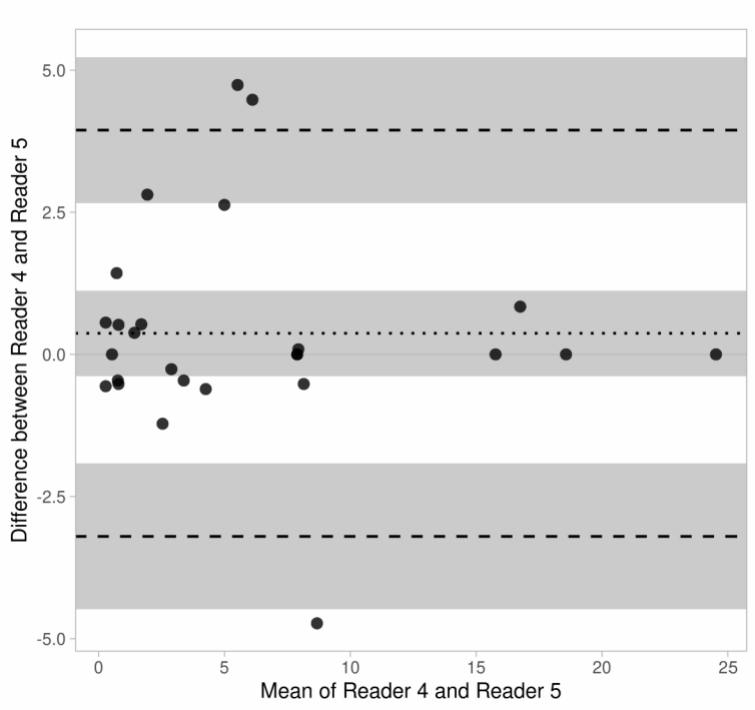

Difference between Reader 2 and Reader 3
4
0
-4
0
10
20
Mean of Reader 2 and Reader 3


Difference between Reader 2 and Reader 4
7.5
5.0
2.5
0.0
-2.5
-5.0
0
10
20
Mean of Reader 2 and Reader 4


Difference between Reader 2 and Reader 5
5
0
-5
0
10
20
Mean of Reader 2 and Reader 5


Difference between Reader 3 and Reader 4
2.5
0.0
-2.5
0
5
10
15
20
25
Mean of Reader 3 and Reader 4


Difference between Reader 3 and Reader 5
6
3
0
-3
0
5
10
15
20
25
Mean of Reader 3 and Reader 5


5.0
2.5
0.0
-2.5
-5.0
Difference between Reader 4 and Reader 5
0
5
10
15
20
25
Mean of Reader 4 and Reader 5

Appendix XII. Conference certificate and presentation poster

Dear Arwa Alhulwah

Mellanby Centre Research Meeting – Friday 25 March 2022 – Snap poster presentation

Thank you for submitting your abstract entitled "**Inter-reader agreement of the skeletal burden score in patients with fibrous dysplasia.**".

I am delighted to inform you that your abstract has been selected for a poster presentation. As well as your poster presentation, you will have **one minute** to present your key finding in one PowerPoint slide (without builds), known as a 'Snap Presentation'. Due to time constraints it is imperative that these timings are strictly adhered to.

Posters will be judged *by timing* for one of the Mellanby Centre's research prizes.

The finalised programme will be circulated in coming weeks.

I would be grateful if you could confirm your acceptance of this invitation to give a Snap presentation and poster presentation to Danièle Swain (mellanbycentre@sheffield.ac.uk) by **Thursday 3 March 2022** at the very latest.

Snap Presentation Guidelines
You have been allocated the time slot of **10.01am** for your presentation. In an effort to facilitate accurate timing, the moderator of each session has been encouraged to enforce this timing strictly! Presentations will take place at Inox Conference Suite, Level 5, Students' Union Building, Durham Road. Each presenter is responsible for their own presentation and should check that the final version is correctly formatted.

Please send your presentation to mellanbycentre@sheffield.ac.uk by **Wednesday 9 March 2022.** This will allow for presentations to be loaded correctly onto the computer and to allow time for formatting problems to be corrected. ***Please note that Mac presentations must be PC compatible, with all images, etc. complete.***

Poster Presentation Guidelines
Please produce a poster to fit in A0 **portrait** sized poster board (1189mm x 841mm wide).

Your allocated snap poster number is **2**, which will be displayed in the top left hand corner of the poster board.

Inter-Reader Agreement of the Skeletal Burden Score in Patients with Fibrous Dysplasia

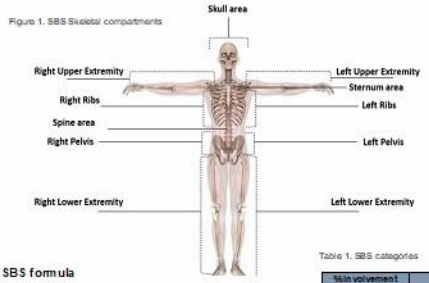
Arwa Alhulwah[1], Sarah Alshahwan[2], Abdulaziz Alsugair[2], Riyadh Al-Salloum[2], Alan Rigby[3], Ashok Raghavan[4], Amaka C. Offiah[1,4]

[1]Department of Oncology & Metabolism, University of Sheffield, Sheffield, UK. [2]Radiology Department, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia. [3]Hull York Medical School, University of Hull. [4]Radiology Department, Sheffield Children's Hospital, Sheffield, UK.

Background

- Fibrous dysplasia (FD) is a rare non-inherited bone disease, in which bone cells are replaced by abnormal fibrous tissue causing many complications.
- Physical impairment and bone pain are the most common reported symptoms in patients with FD.
- A measurement of skeletal severity is the Skeletal Burden Score (SBS) created by Collins *et al*, 2005 [1].

Figure 1. SBS Skeletal compartments



The SBS formula

$$(18.4\% \times \text{skull area}) + [19\%(\text{right upper extremity} + \text{left upper extremity}) \div 2] + [42\%(\text{right lower extremity} + \text{left lower extremity}) \div 2] + (8.3\% \times \text{spine area}) + [4.4\%(\text{right ribs} + \text{left ribs}) \div 2] + (8.3\% \times \text{sternum area}) + 7.4\%(\text{right pelvis} + \text{left pelvis}) \div 2$$

Table 1. SBS categories

%Involvement	Score
0 %	0
0-5%	2.5%
5-25 %	15%
25-50	37.5%
< 50 %	75%

Objectives

- The FD/MAS* international consortium recommendations are that the skeletal burden score (SBS) should be used to assess severity of skeletal involvement in patients with fibrous dysplasia.
- The purpose of this study was to evaluate the inter-reader agreement of the SBS amongst radiologists with varying speciality and experiences from the United Kingdom and Saudi Arabia.

Methods

- **5** readers scored **26** NM bone scans from consented KFSHRC* and KFSH* patients in Saudi Arabia.
- The readers were blinded to the clinical history and scored the cases independently.
- Inter-reader agreement was investigated using Bland-Altman plots of the SBS scores, and the intra-class correlation coefficient (ICC) (overall reliability).

Table 2. Reader speciality and experience

Reader	Speciality , Location	Years of Experience
Reader 1	Consultant Paediatric Radiologist, UK	19 Years
Reader 2	Consultant Paediatric Radiologist, UK	16 Years
Reader 3	Consultant Radiologist, Nuclear Medicine Fellowship, SA	5 Years
Reader 4	Consultant Nuclear Medicine Physician, SA	25 Years
Reader 5	Consultant Nuclear Medicine Radiologist, Paediatric Nuclear Medicine Fellowship, SA	10 Years

Results

Figure 2. Overall reader scores

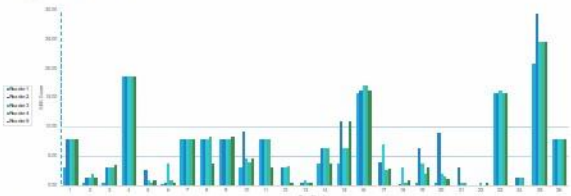


Table 3. Reported SBS scores of this case

Skeleton segments	1	2	3	4	5
Skull area	0	0	0	0	0
Sternum	0	0	0	0	0
Rt. Ribs	0	0	0	0	0
Lt. Ribs	0	0	0	0	0
Rt. Upper. Extrem.	0	0	0	0	0
Lt. Upper. Extrem.	0	0	0	0	0
Spine	0	0	0	0	0
Rt. Pelvis	0	0	0	0	0
Lt. Pelvis	0	0	0-5%	0	0
Rt. Lower Extrem.	0-5%	5-25%	5-25%	5-25%	0-5%
Lt. Lower Extrem.	5-25%	5-25%	5-25%	5-25%	5-25%
Total SBS	3.68	6.31	6.40	6.31	3.68

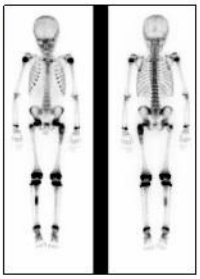
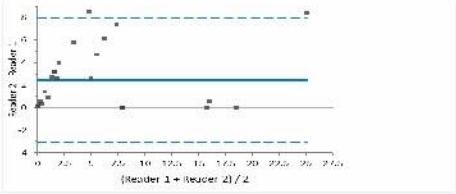


Figure 4&5. Selected Bland-Altman Plots



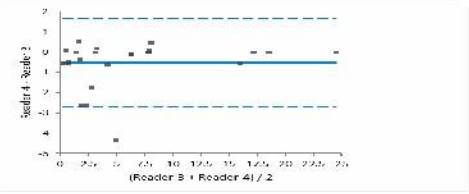


Table 4. Inter-Item Correlation Matrix

	Reader 1	Reader 2	Reader 3	Reader 4	Reader 5
Reader 1	-	0.910	0.961	0.978	0.934
Reader 2	0.910	-	0.930	0.942	0.944
Reader 3	0.961	0.930	-	0.985	0.957
Reader 4	0.978	0.942	0.985	-	0.961
Reader 5	0.934	0.944	0.957	0.961	-

Conclusion

- This the first study to measure inter-reader agreement among radiologists/nuclear medicine physicians using SBS.
- A high degree of reliability was found between readers. The average measure ICC was **0.986** with a 95% confidence interval from 0.971 to 0.993 ($F(25,100)= 93.410$, $p<.001$).
- The preliminary results of this study suggest an excellent reader reliability of the SBS, and high reader agreement.
- No significant variation between speciality and experience.
- Intra-reader reliability was not assessed.

Reference:

1- Collins MT, Kushner H, Reynolds JC, et al. An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. *J Bone Miner Res*. 2005;20(2):219-226.

Acknowledgments:

- We would like to thank Dr. Michael Collins for his support in conducting this study.

*MAS = McCune-Albright syndrome, *KFSH = King Fahad Specialist Hospital, SA
*KFSHRC = King Faisal Specialist Hospital & Research Centre, SA

What Is the Correlation Between Skeletal Burden Score and Functional Outcomes in Fibrous Dysplasia?:A Systematic Review

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Background

- Fibrous dysplasia (FD) is a rare non-inherited genetic disease, in which healthy bone cells are replaced by fibrous tissue.
- FD can cause bone pain, pathological fractures, scoliosis, bone deformity and functional disabilities [1,2].
- Fibrous dysplasia may occur as a single (monostotic FD) or multiple lesions (polyostotic FD).
- Polyostotic FD may be associated with extra-skeletal manifestations including café-au-lait spots, precocious puberty and hyperthyroidism; this condition is called McCune-Albright syndrome (MAS).
- Functional abilities in children with FD decline as they enter adulthood [3].
- Bone turnover markers (BTM) such as alkaline phosphate and osteocalcin are unreliable measurements of disease severity as they change with age and with the use of bisphosphate treatment.
- Severity of skeletal involvement and bone pain have the most negative impact on the quality of life. Skeletal severity can be quantified using the Skeletal Burden Score (SBS)[1].
- The SBS is based on calculations derived from ^{99m}Tc-MDP nuclear medicine bone scans. The score ranges from 0 to 75, a high score indicates severe skeletal burden [1].
- Little attention has been given to the impact of FD on the patient's functional outcomes and quality of life (QoL).

Objectives

To determine the correlation between the skeletal burden score (SBS) - as calculated from nuclear medicine bone scans - and functional outcomes in children and adults with fibrous dysplasia.

Methods

- A systematic review was conducted to determine the ability of the SBS to predict functional outcomes in patients with fibrous dysplasia.
- PubMed, SCOPUS, Web of Science, Ovid MEDLINE and The Cochrane Library were searched from February 2005 up to April 2020. Reference lists of the retrieved papers were screened for additional relevant papers.

Inclusion criteria:

- Children and adults with radiological, histological, or genetic confirmation of fibrous dysplasia.
- Studies including the use of validated questionnaires to asses functional and physical abilities in patients with fibrous dysplasia.

Exclusion criteria:

- Studies that did not use the SBS to measure skeletal severity, clinical trials, review papers, case studies, non-English language papers, conferences and meeting abstracts with no full-texts.

Results

A total of 166 articles were retrieved from the four databases. Only 7 articles met the inclusion criteria and were included in the systematic review.

Figure 1: PRISMA Flowchart

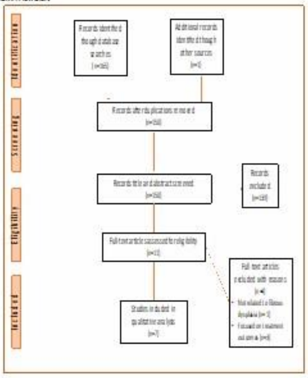

Table 1: Characteristics of included studies

Authors, year	Country	Sample Size	Age Range	Study Type*	FD Type	QoL Measurement Tool	Predictors
Collins (2005)	USA	79	(4-80)	Cross sectional	All FD forms	SF-36, CHQ-PF50	SBS, BTM, ambulatory status
Hart (2007)	USA	109	(1-84)	Cohort study	All FD forms	Medical notes (functional status)	SBS, ambulatory status
Kelly (2005)	USA	78	(6-80)	Cohort study	All FD forms	SF-36, CHQ-PF50	SBS, ambulatory status
Leet (2006)	USA	27	(2-16)	Cohort study	Polyostotic FD	PODCI	SBS, presence of fractures, scoliosis
Majoor (2017a)	Netherlands	97	(16-60)	Retrospective	All FD forms	SF-36, BPI	SBS, FGF-23 levels, BTM
Majoor (2017b)	Netherlands	97	(16-60)	Retrospective	All FD forms	SF-36, IPQ-R, BPI	SBS, FGF-23 levels, age, gender
Rotman (2018)	Netherlands	92	(16-60)	Cross sectional	All FD forms	UCL, SF-36, BPI	SBS, BTM, Fracture, surgery history

QoL = Quality of life, FD = Fibrous dysplasia, IPQ-R = Illness Perception Questionnaire Revised, BPI = Brief Pain Inventory, PODCI = Paediatric Outcomes Data Collection Instrument, UCL = Utrecht Coping List Questionnaire: UCL.

Table 2: QoL Reported functional and pain scores

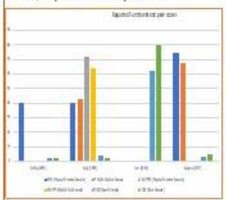

Table 3: Correlation of SBS with outcome factors

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

- Although most studies did not include statistical analysis data on SBS, QoL scores or functional status, a relationship between high SBS and functional impairment was concluded by studies [1,4,6,7].
- Children with higher SBS (>30) had greater functional impairment and a need for ambulatory assistance (canes, crutches or wheelchair) in adulthood.
- Studies using SF-36/CHQ-PF50 to measure quality of life reported lower scores in the physical function and bodily pain domains compared with their standard reference populations [1,4,6,7].
- One study [5] using the Paediatric Outcome Data Collection Instrument (PODCI), found a correlation between sport scale scores and femoral neck-shaft angle, but no correlation between any of the PODCI scales and SBS, endocrine dysfunction, number of fractures or Cobb angle (in children with scoliosis).
- The study by Rotman et al [8], showed that passive coping strategies and illness perception were a major determinant of QoL in patients with FD.

Conclusions

This systematic review demonstrates that there is a limited focus on understanding the impact of fibrous dysplasia (FD) on patient functional abilities and overall quality of life. Results of this systematic review suggest that skeletal burden score (SBS) is a precise indicator of FD severity and has potential to assess future functional outcomes in children with FD. A follow-up longitudinal study is recommended to evaluate the predictive power of SBS for long-term functional outcomes in children with FD.

References

1. Collins MT, Kushner H, Reynolds JC, et al. An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. J Bone Miner Res. 2005;20(2):219-226.
2. DiCaprio, M.R. and W.F. Enneking. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J Bone Joint Surg Am., 2005. 87(8):1848-64.
3. Hart, Elizabeth S, Kelly, Marilyn H, Brillante, Beth, Chen, Clara C, Ziran, Navid, Lee, Janice S, Feuillan, Penelope, Leet, Arabella I, Kushner, Harvey, Robey, Pamela G, and Collins, Michael T. "Onset, Progression, and Plateau of Skeletal Lesions in Fibrous Dysplasia and the Relationship to Functional Outcome." Journal of Bone and Mineral Research 22.9 (2007): 1468-474. Web.
4. Kelly, Marilyn H, Brillante, Beth, Kushner, Harvey, Gehron Robey, Pamela, & Collins, Michael T. (2005). Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone. Bone (New York, N.Y.), 37(3), 388-394.
5. Leet, Arabella I, Wientroub, Shlomo, Kushner, Harvey, Brillante, Beth, Kelly, Marilyn H, Robey, Pamela Gehron, & Collins, Michael T. (2006). The Correlation of Specific Orthopaedic Features of Polyostotic Fibrous Dysplasia with Functional Outcome Scores in Children. Journal of Bone and Joint Surgery. American Volume, 88(4), 818-823.
6. Majoor, Bas C.J., Andela, Cornelie D, Bruggemann, Jens, Van De Sande, Michiel A. J, Kaptein, Ad A, Hamdy Neveen A. T, ... Appelman-Dijkstra, Natasha M. (2017). Determinants of impaired quality of life in patients with fibrous dysplasia. Orphanet Journal of Rare Diseases, 12(1), 80.
7. Majoor, B.C. J, Andela, C.D, Quispel, C.R, Rotman, M, Dijkstra, P.D. S, Hamdy, N.A.T, ... Appelman-Dijkstra, N.M. (2018). Illness Perceptions are Associated with Quality of Life in Patients with Fibrous Dysplasia. Calcified Tissue International, 102(1), 23-31.
8. Rotman, M. (2017). Passive Coping Strategies Are Associated With Higher Impairment In Quality Of Life In Patients With Fibrous Dysplasia (Vol. 32).

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