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FRAX predictions in upper extremity fracture and non-fracture patients

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Thesis

**FRAX PREDICTIONS IN UPPER EXTREMITY FRACTURE AND NON-
FRACTURE PATIENTS**

by

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THANY SEYOK

ABSTRACT

Osteoporosis is the most common human bone disease and a growing public health problem. Worldwide, 9 million fractures due to osteoporosis occur annually. Fracture is the main burden of the disease and is linked with significant morbidity and mortality. A history of upper extremity fragility fracture is known to contribute to increased risk of subsequent fractures. In this study, we compared the estimated FRAX 10-year probability of major osteoporotic fracture and hip fracture between upper extremity (UE) fracture and non-fracture patients. In addition, we assessed differences in demographics and osteoporosis evaluation between the two groups, and we report the prevalence of lab abnormalities among UE fragility fracture patients evaluated in our fracture liaison service (FLS). A total of 243 patients from Brigham and Women's Faulkner Hospital were recruited to participate in the study. UE fracture patients were recruited from our FLS, and UE non-fracture patients were recruited from the UE clinic. Overall 10-year probability of major osteoporotic and hip fracture was higher in upper extremity fracture patients than upper extremity non-fracture patients (19.23 versus 9.23, $p < 0.001$ and 4.26 versus 1.54, $p < 0.001$ respectively). When excluding fragility fracture history, 10-year probability of major osteoporotic fracture and hip fracture were similar

between upper extremity fracture and non-fracture patients (10.59 versus 9.23, $p = 0.095$ and 1.88 versus 1.54, $p = 0.215$ respectively). The proportion of osteoporosis evaluation via bone mineral density assessment was higher in upper extremity fracture patients compared to upper extremity non-fracture patients ($p < 0.001$). However, the proportion of upper extremity fracture patients on osteoporosis medication was low and not different than upper extremity non-fracture patients ($p < 0.079$). Our results highlight history of fragility fracture as an important driver in subsequent fracture risk. UE fracture and non-fracture patients harbor similar fracture clinical risk factors, with the exception of fracture history, and are similarly at risk for future hip fracture and major osteoporotic fracture. Our results suggest close osteoporosis evaluation of older upper extremity non-fracture patients is warranted.

TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vii
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION	1
OSTEOPOROSIS	1
FRAGILITY FRACTURE.....	2
FRAGILITY FRACTURE RISK FACTORS.....	5
OSTEOPOROSIS SCREENING.....	11
FRACTURE LIAISON SERVICES.....	19
SPECIFIC AIMS.....	21
METHODS	22
PARTICIPANTS.....	22

STUDY OUTCOMES.....	22
FRAX CALCULATOR.....	23
LAB ABNORMALITIES.....	23
STATISTICAL ANALYSIS.....	24
RESULTS	25
SUBJECT CHARACTERISTICS.....	25
LAB ABNORMALITIES.....	26
FRAX SCORES.....	27
FRACTURE RISK FACTORS.....	28
OSTEOPOROSIS EVALUATION AND TREATMENT.....	29
DXA T-SCORES.....	30
DISCUSSION	32
APPENDIX.....	38
REFERENCES	41
CURRICULUM VITAE.....	54

LIST OF TABLES

Table	Title	Page
1	Summary of fragility fracture risk factors	11
2	WHO diagnostic criteria	12
3	Analytic cohort characteristics	26
4	FRAX scores	27
5	Clinical risk factors	28
6	Osteoporosis evaluation and treatment	29
7	Mean DXA T-scores	30
8	Data completion status (Men and Women)	38
9	Data completion status (Women Only)	38
10	Risk factors associated with fracture (Women Only)	39
11	Osteoporosis evaluation and treatment (Women Only)	40
12	Number of DXA T-scores available (Men and Women)	40

LIST OF FIGURES

Figure	Title	Page
1	Glucocorticoid effects on BMD	9
2	FRAX® online user interface	14
3	Garvan Fracture Risk Calculator online user interface	16
4	QFractureScores online user interface	17
5	Selection of analytic cohorts	25
6	DXA T-scores box and whisker plot	31

LIST OF ABBREVIATIONS

BMD.....	Bone Mineral Density
BPF.....	Best Practice Framework
BWHF.....	Brigham and Women’s Faulkner Hospital
CF.....	Cystic Fibrosis
CT.....	Computer Tomography
DXA.....	Dual-Energy X-Ray Absorptiometry
FLS.....	Fracture Liaison Service
IBS.....	Inflammatory Bowel Syndrome
IOF.....	International Osteoporosis Foundation
MRI.....	Magnetic Resonance Imaging
NOF.....	National Osteoporosis Foundation
PTH.....	Parathyroid Hormone
RA.....	Rheumatoid Arthritis
SD.....	Standard Deviation
UE.....	Upper Extremity
USPSTF.....	United States Preventative Services Task Force
VFF.....	Vertebral Fragility Fracture
WHO.....	World Health Organization

INTRODUCTION

Osteoporosis

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural disruption resulting in skeletal fragility and increased risk for fractures. Osteoporosis is the most common human bone disease affecting an estimated 200 million people worldwide (Cooper, Campion, & Melton, 1992). In the United States, an estimated 10.2 million adults over the age of 50 have osteoporosis, and another 43.4 million are at risk for developing osteoporosis due to harboring osteopenia; low bone mass (Wright et al., 2014). As the population in the United States continues to age, the prevalence of osteoporosis is projected to rise as much as 50% by 2025 (Kling, Clarke, & Sandhu, 2014).

Fracture is the major burden of osteoporosis and drastically changes the quality of life for patients and their families due to limitation of ambulation, depression, loss of independence, chronic pain, and economic burden (Adachi et al., 2010). Annually, approximately 9 million fractures occur worldwide due to osteoporosis, with the majority of them occurring in developed countries (O. Johnell & Kanis, 2006). The economic burden resulting as a consequence of fragility fractures are enormous for western populations and are expected to dramatically increase in Asia, Latin America and the Middle East as populations continue to age. The total direct cost of fragility fractures in Europe was 32 billion euros in 2005 (J. A. Kanis & Johnell, 2005). In the USA, the combined cost of all fragility fractures in 2002 was \$20 billion (Steven R. Cummings &

Melton, 2002). In 2006, China spent an estimated \$1.6 billion on hip fracture care, which is projected to increase to \$265 billion by 2050 (Mithal, Bansal, Kyer, & Ebeling, 2014). Being a silent disease, many patients are unaware they have osteoporosis until they sustain a fragility fracture.

Fragility Fracture

Fragility fractures, also referred to as osteoporotic or low-trauma fractures, are fractures that result from a fall of standing height or less without major trauma. Among older adults in the United States, fragility fractures have become nearly epidemic with an estimated 2 million occurring each year (Singer et al., 2015). Fragility fractures are more common in women than men, due in part to the decline in estrogen, which has a protective effect on bone mass, associated with menopause in women (Riggs, Khosla, & Melton, 1998). The lifetime risk for fragility fracture is 40% to 50% and 13% to 22% for women and men, respectively (Olof Johnell & Kanis, 2005). Half of all women over 50 years old and one-fifth of all men over 50 years old are expected to experience a fragility fracture in their lifetime (J. A. Kanis & Glüer, 2000). Fragility fractures typically occur at the vertebrae (spine), proximal femur (hip), proximal humerus (shoulder), or distal radius (wrist).

Vertebral fragility fractures (VFFs) are the most common type of fragility fractures and serve as strong predictors of future fractures at any site independent of bone mineral density (BMD) (P. D. Delmas et al., 2003). VFFs occur in 30% to 50% of people over the age of 50 years old and significantly increases the risk for subsequent VFFs

(Briggs, Greig, & Wark, 2007; Melton et al., 1993), resulting in a phenomenon referred to as the “vertebral fracture cascade”. VFFs can occur independent of a fall, and symptoms include chronic back pain, height loss, and spinal deformity. Diagnosis is confirmed via imaging performed specifically to examine the spine, or incidentally from images performed for other clinical indications, such as abdominal computed tomography (CT) or magnetic resonance imaging (MRI) (Adams, 2016). Approximately 30% of VFFs are asymptomatic and do not come to clinical attention (Ensrud, 2013). In addition, it has been reported that VFFs are generally under-diagnosed radiographically by radiologists worldwide (Pierre D. Delmas et al., 2005). Therefore, a large proportion of patients with VFFs may not be receiving appropriate osteoporosis evaluation or treatment putting them at higher risk for severe fractures such as hip fractures.

Among fragility fractures seen in men and women over the age of 50, hip fractures cause substantial morbidity and mortality (Haleem, Lutchman, Mayahi, Grice, & Parker, 2008). Worldwide, it is estimated over 1.7 million people aged 50 years old or older suffer from hip fractures, and that number is expected to increase to 6.3 million by 2050 (Cooper et al., 1992). In patients aged 65 and over that sustain a hip fracture, the one-year mortality risk has been estimated to be 12% to 37%, and the 5-year mortality risk can reach 60% in some elderly populations (Tajeu et al., 2014). Among those that survive a hip fracture incident, half do not regain their pre-fracture functionality, and approximately 20% require some form of long-term care (Office of the Surgeon General (US), 2004). Hip fractures are seldom the initial fracture event seen in osteoporotic patients. It has been reported that approximately half of hip fracture patients suffered

prior fracture events before sustaining the hip fracture (Edwards, Bunta, Simonelli, Bolander, & Fitzpatrick, 2007; Port et al., 2003). Indeed, the initial fragility fracture should serve as a warning and lead to osteoporosis screening and treatment initiation, if warranted, to prevent subsequent refractures (Cosman et al., 2014).

The most common sites for upper extremity fragility fractures are in the distal radius and proximal humerus. Distal radius fractures often occur as a result of attempting to provide protection during a fall by using the hands, and proximal humerus fractures often occur as a result of direct falls onto the shoulder joint (Kelsey, Browner, Seeley, Nevitt, & Cummings, 1992). Distal radial fractures are more common in women who have low BMD, are more active, and relatively healthy. Proximal humeral fractures are more common in women who have a low BMD and who are less active (Kelsey et al., 1992). The incidence of distal radial fractures is approximately 100–130 per 100,000 people per year and 300–400 per 100,000 people per year for men and women, respectively (Kelsey et al., 1992). In men, the incidence of distal radial fractures does not increase with age. In women, the incidence increases throughout their late 50s and tends to decrease after the age of 85 (Kelsey et al., 1992). Although the direct consequences of distal radius and proximal humerus fractures are less severe than hip fractures, they serve as predictors for future fractures, including hip fractures (Jung et al., 2019). One study estimated that a single proximal humeral fracture increases the risk of a subsequent hip fracture more than five times in the first year after the humeral fracture (Clinton et al., 2009). Indeed, early signs of upper fractures should trigger appropriate evaluation and treatment for osteoporosis to prevent subsequent fractures.

Fragility Fracture Risk Factors

Low bone strength is one of the strongest predictors for fragility fracture. Properties that make up bone strength include bone mineral density (BMD), bone microarchitecture, bone size and shape, bone turnover, and degree of bone mineralization (Ahlborg, Johnell, Turner, Rannevik, & Karlsson, 2003). The most widely used method for measuring BMD is Dual-energy x-ray absorptiometry (DXA). DXA measures bone mineral content (in grams) and bone area (in square centimeters) and calculates an areal BMD, expressed in g/cm^2 . DXA also reports BMD as a T-score, defined as the difference in number of standard deviations (SDs) from the mean BMD of a normally distributed healthy adult reference population, typically an average healthy 30-year old adult (“Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group,” 1994). In addition, BMD is also reported as a Z-score, which is calculated similarly to the T-score but uses an age-matched normal population for comparison (Lewiecki et al., 2004). DXAs are typically performed at skeletal sites associated with major clinical consequences if a fracture were to occur at that site. These skeletal sites include the spine, hip, and forearm. Numerous studies have demonstrated that low BMD measured by DXA at any skeletal site can predict fragility fracture (Black et al., 1992; Olof Johnell et al., 2005; Leslie, Tsang, Caetano, Lix, & Manitoba Bone Density Program, 2007; Stone et al., 2003). However, site-specific measurements are typically better predictors for fractures at their respective sites (Marshall, Johnell, & Wedel, 1996). For example, results from a DXA of the hip are a

better predictor for future hip fracture than results from a DXA of the forearm or spine. In general, prior studies have shown that a one standard deviation decrease in BMD results in an approximately twofold increase in risk of fragility fracture (Cauley et al., 2007; Leslie et al., 2007).

In addition to BMD, a number of clinical risk factors also provide information on fracture risk. These clinical risk factors include falls, advancing age, family history of hip fracture, smoking history, excessive alcohol consumption, low body weight, history of fragility fracture, glucocorticoid therapy, rheumatoid arthritis and secondary osteoporosis (John A. Kanis, 2002).

For any given BMD T-score of the femoral neck, the probability of hip fracture increases with age (J. A. Kanis et al., 2001). Additionally, a history of fragility fracture in a first-degree relative is associated with increased risk of fracture. Cummings et al. (1995) reported that parental history of hip fracture was associated with a twofold-increased risk of hip fracture in women regardless of BMD (S. R. Cummings et al., 1995). Meta-analyses conducted by Kanis et al. (2005) showed that cigarette smoking is associated with decreased BMD and increase risk of fracture (J. A. Kanis et al., 2005). The risk was higher in current smokers compared to those with a smoking history. The increased risk of fracture associated with excessive alcohol intake is dose dependent (John A. Kanis, Johansson, et al., 2005). Consumption of over 28 grams of pure alcohol, equal to about over two drinks per day was shown to be associated with an increased risk of hip fracture (RR 1.39, 95% CI 1.08-1.79) (Berg et al., 2008).

Low body weight, less than 58kg or 127lb, is associated with increased risk of osteoporosis and fracture (Green, Colón-Emeric, Bastian, Drake, & Lyles, 2004). In women, height increase and weight loss after 50 increases the risk of hip fracture, while weight gain decreases the risk of hip fracture (Meyer, Falch, O'Neill, Tverdal, & Varlow, 1995). Interestingly, the method in which weight is lost may affect bone physiology. A randomized trial reported subjects who lost weight via calorie restriction had decreased total hip BMD, while subjects who lost the same amount of weight via exercise without calorie restriction had no changes in BMD (Villareal et al., 2006).

A history of a fragility fracture is an important risk factor for subsequent fracture in men and women. Kanis et al. (2004) conducted a meta-analysis of 11 prospective cohort studies from around the world on fracture risk in men and women with a history of fracture and reported increased risks for any fracture (relative risk (RR) 1.8, 95% CI 1.6-1.9), osteoporotic fracture (RR 1.8, 95% CI 1.6-1.9), and hip fracture (RR 1.6, 95% CI 1.3-2.0) (J. A. Kanis et al., 2004). A history of a high-trauma fracture may also be a risk factor for subsequent fracture in women. A nine-year study of 8022 women participating in The Study of Osteoporotic Fractures reported an increased risk of subsequent fracture in women with a previous history of high and low trauma non-spine fractures compared with women who had not had such fractures (Mackey et al., 2007). The risk of subsequent fracture was 34 percent (95% CI 7-67) and 31 percent (95% CI 20-43) higher among women with a history of high and low trauma fracture, respectively.

Glucocorticoid therapy is associated with marked increase in risk of bone loss and fracture (van Staa, Leufkens, & Cooper, 2002). Glucocorticoids particularly increases the

risk of vertebral fracture during the earlier stages of the glucocorticoid therapy, which are typically associated with a rapid phase of bone loss (Angeli et al., 2006). BMD levels of fracture patients on glucocorticoid therapy are typically higher than fractures seen in patients with postmenopausal osteoporosis (Canalis, Mazziotti, Giustina, & Bilezikian, 2007). Fractures have been reported in as many as 30 to 50 percent of glucocorticoid users, and the incidence of fracture are higher with advanced age, larger doses, and longer durations of glucocorticoid therapy (Canalis et al., 2007; Curtis et al., 2006). However, an increased risk of fracture has also been reported with low doses of prednisone, a commonly prescribed glucocorticoid, or its equivalent even as low as 2.5 to 7.5 mg daily and with short-term use, defined as less than 30 days of use (Van Staa, Leufkens, Abenhaim, Zhang, & Cooper, 2000; Waljee et al., 2017). The detrimental effects of glucocorticoid on bone result from its direct effects on osteoblasts and osteoclasts. Osteoblasts and osteoclasts are bone cells responsible for bone formation and bone resorption respectively. Glucocorticoids increase osteoclast activity and reduce osteoblast activity (**Figure 1**) (Canalis et al., 2007). The risk of bone loss is typically significantly greater in the first months of use followed by slower loss of bone with continued use (Canalis et al., 2007). With continued use, osteoclast-mediated resorption of bone slows, and suppression of bone formation becomes the major effect on bone. In addition, glucocorticoids also decrease intestinal calcium absorption by opposing the actions of vitamin D and by decreasing the expression of calcium channels in the duodenum (Huybers, Naber, Bindels, & Hoenderop, 2007).

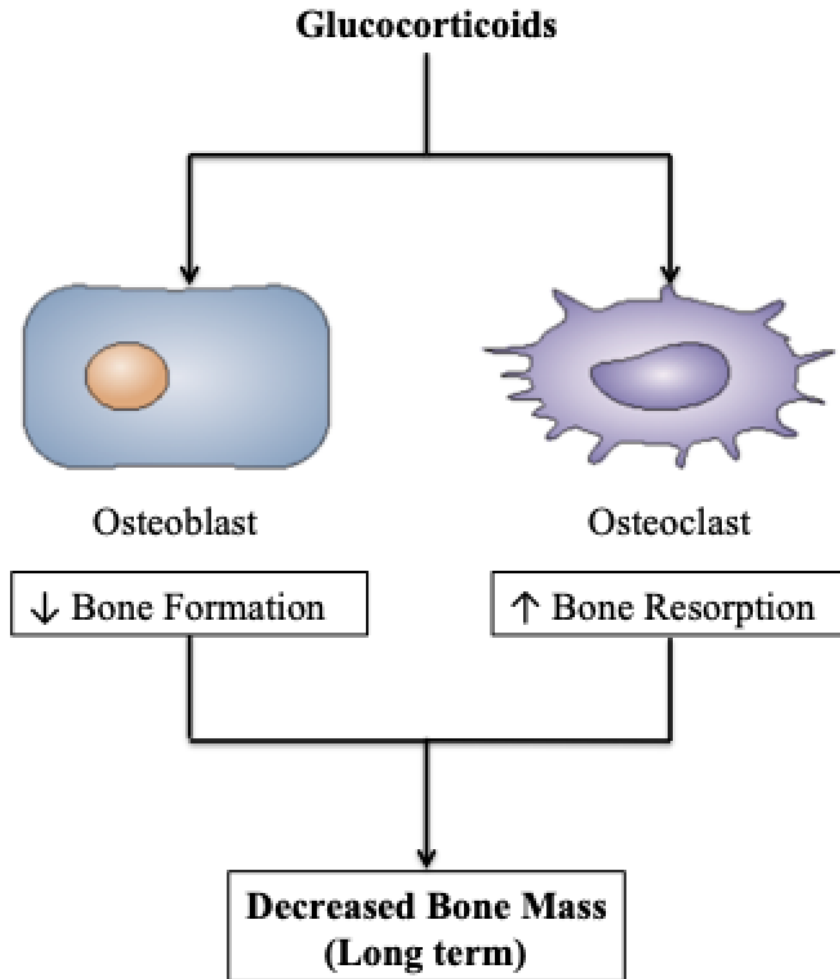


Figure 1. Glucocorticoid effects on BMD.

In addition to BMD and non-BMD risk factors, medical diseases associated with low BMD also increase fracture risk. These medical diseases include rheumatoid arthritis (RA), inflammatory bowel disease (IBS), celiac disease, cystic fibrosis (CF), hyperthyroidism, type 1 and 2 diabetes, renal diseases, and sickle cell disease (Deal,

2012; Ensrud et al., 2007; Grey et al., 2008; Kemppainen et al., 1999; Targownik et al., 2013; Thong et al., 2018; Vanderhave, Perkins, Scannell, & Brighton, 2018; Vestergaard & Mosekilde, 2003). These diseases typically contribute to low BMD through underlying inflammation, malabsorption, renal excretion of calcium, or secondarily via medications used to treat these diseases. Other risk factors include vitamin D deficiency, dementia, history of breast cancer, and use of select medications including androgen deprivation agents, aromatase inhibitors, proton pump inhibitors, selective serotonin reuptake inhibitors, thiazolidinediones, and anticonvulsants (Lakkireddy, Mudavath, Karra, & Arora, 2019; Mughal, Inderjeeth, & Inderjeeth, 2019; Watts, 2017).

Potential risk factors for increased fracture have also been identified. These include depression, mild asymptomatic hyponatremia (serum sodium <135 mEq/L), aortic calcification on computed tomography (CT) scan, high levels of inflammation markers, high dietary retinol intake, sedentary lifestyle, vitamin B12 deficiency, high homocysteine concentrations, large amounts of caffeine consumption, and intake of carbonated beverages (S. R. Cummings et al., 1995; Gankam Kengne, Andres, Sattar, Melot, & Decaux, 2008; Gregg, Cauley, Seeley, Ensrud, & Bauer, 1998; Leboff et al., 2009; Macêdo, Carvalho, Cavalcanti, & Freitas, 2017; Mezuk, Eaton, & Golden, 2008; Schett et al., 2006; Schulz, Arfai, Liu, Sayre, & Gilsanz, 2004; Tucker et al., 2006; Zhang et al., 2017)

Table 1. Summary of fragility fracture risk factors

Clinical Risk Factors	Advanced age Familial hip fracture Smoking history Excessive alcohol intake Low body weight Fragility fracture history Glucocorticoid therapy Vitamin D deficiency
Medical Diseases	Rheumatoid arthritis Inflammatory bowel syndrome Celiac disease Cystic fibrosis Hyperthyroidism Type I and II diabetes Renal diseases Sickle cell
Potential Risk Factors	Depression Mild asymptomatic hyponatremia Aortic calcification High inflammation markers High retinol intake Sedentary lifestyle Vitamin B12 deficiency High homocysteine levels Excessive caffeine intake Intake of carbonated beverages

Osteoporosis Screening

The World Health Organization (WHO) published the first diagnostic criteria for osteoporosis in 1994 using epidemiological data (**Table 2**). The WHO defines normal bone as BMD T-scores no more than 1 SD below the average, osteopenia as BMD T-scores 1 to 2.5 SDs below the average, osteoporosis as BMD T-scores greater than 2.5

SDs below the average, and severe osteoporosis as BMD T-scores greater than 2.5 SDs below average with a history of one or more fragility fractures (J. A. Kanis, 1994).

Table 2. WHO diagnostic criteria

Classification	BMD
Normal	A value for BMD within 1.0 SD of the young adult female reference average (T-score greater than or equal to -1.0 SD).
Osteopenia (low bone mass)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference average (T-score less than -1 and greater than -2.5 SD).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference average (T-score less than or equal to -2.5 SD).
Severe osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference average in the presence of one or more fragility fractures (T-score less than or equal to -2.5 SD).

**BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; SD = standard deviation*

The National Osteoporosis Foundation (NOF) and United States Preventive Services Task Force (USPSTF) both recommend DXA BMD screening in all postmenopausal women age 65 years or older regardless of risk factors (Cosman et al., 2014; US Preventive Services Task Force et al., 2018). There is no universal agreement regarding DXA BMD screening in older men. The USPSTF found insufficient evidence to make a recommendation for screening men (US Preventive Services Task Force et al.,

2018). However, other groups including the NOF have recommended DXA BMD screening for all men older than 70 years old (Cosman et al., 2014). For men and women under 65 years old, DXA BMD screening recommendations vary. For women younger than 65 years, The USPSTF recommends DXA BMD screening for individuals who are at increased risk for osteoporosis as determined by clinical risk assessment tools (US Preventive Services Task Force et al., 2018).

The most widely used tool to assess fracture risk is FRAX®. The FRAX® tool was developed in 2008 by researchers at The University of Sheffield to estimate fracture risk in untreated patients between the ages of 40 and 90 years old using easily obtainable fracture clinical risk factors and femoral neck DXA BMD (J. A. Kanis, Johnell, Oden, Johansson, & McCloskey, 2008). FRAX® is based on data collected from large, prospective, observational studies that evaluated clinical risk factors, BMD, and fractures in men and women of different ethnicities and from different regions of the world (John A. Kanis, Borgstrom, et al., 2005). FRAX® has been validated in 26 independent cohorts comprised of mainly women (Marques et al., 2015). The statistical power of this large dataset allows estimation of a 10-year probability of hip fracture, and major osteoporotic fracture at the spine, forearm, and shoulder from an individual's set of risk factors. Clinical risk factors accounted for by the tool include country of residence, ethnicity, age, sex, weight, height, fragility fracture history, parental hip fracture history, current smoking status, glucocorticoid use, rheumatoid arthritis diagnosis, secondary osteoporosis diagnosis, and excessive alcohol consumption. In addition, the FRAX® tool can also be used to assess fracture risk when a femoral neck BMD is not available.

FRAX® predictions solely on clinical factors have been shown to provide the same risk predictions as FRAX® predictions with both clinical factors and femoral neck BMD in most cases (Gadam, Schlauch, & Izuora, 2013). This is particularly useful in world regions that do not have access to BMD screening technologies. The FRAX® tool can be accessed online for free at <https://www.sheffield.ac.uk/FRAX/>. The FRAX® tool is also available on mobile devices and newer DXA software.

The screenshot displays the FRAX® online user interface. At the top, it shows the country as 'US (Caucasian)' and a field for 'Name/ID:'. A link for 'About the risk factors' is visible in the top right. The main section is titled 'Questionnaire:' and contains 12 numbered items. Item 1 asks for age or date of birth, with separate fields for age and date (Y, M, D). Item 2 is for sex, with radio buttons for 'Male' and 'Female'. Items 3 and 4 are for weight (kg) and height (cm), each with a text input field. Items 5 through 11 are binary questions with 'No' (selected) and 'Yes' radio buttons: 5. Previous Fracture, 6. Parent Fractured Hip, 7. Current Smoking, 8. Glucocorticoids, 9. Rheumatoid arthritis, 10. Secondary osteoporosis, and 11. Alcohol 3 or more units/day. Item 12 is 'Femoral neck BMD (g/cm²)', which includes a dropdown menu labeled 'Select BMD' and a text input field. At the bottom right of the questionnaire area are 'Clear' and 'Calculate' buttons.

Figure 2. FRAX® online user interface

Other fracture risk assessment tools include the Garvan Fracture Risk Calculator and QFractureScores, which are country specific alternatives to FRAX®. The Garvan calculator was derived using the Australian Dubbo cohort of approximately 2000 men and women, and it predicts osteoporotic fracture risk over 5 or 10 years (Nguyen, Frost, Center, Eisman, & Nguyen, 2008). The 5-year fracture risk prediction is thought to be more useful for patients at older ages. To estimate osteoporotic fracture risk, the Garvan calculator takes into account age, sex, history of fractures since the age of 50, falls over the last 12 months, and BMD measureme. The tool is accessible freely online at <https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/> (**Figure 3**). The QFractureScores was developed and validated through studying primary care populations in the United Kingdom (Hippisley-Cox & Coupland, 2009). The tool estimates risk of osteoporotic fracture over 1 to 10 years and takes into account 30 fracture clinical risk factors (**Figure 4**). However, the tool does not incorporate BMD measurements into their estimates. QFractureScores is also free and accessible at <https://qfracture.org/>.

FRACTURE RISK CALCULATOR

Fill out the following to estimate your fracture risk

Full Name
(optional)

Sex? **Male**
 Female

Age

Fractures since the age of 50
(excluding major trauma, e.g. car accidents)

Falls over last 12 months

Do you have a Bone Mineral Density (BMD) measurement? **Yes**
 No

T-scores ?

OR

Densitometer **by DXA GE Lunar**
 by DXA Hologic

Actual BMD g/cm²

Disclaimer

The results produced by our calculator should serve as a guide only. If concerned about your fracture risk, it is also important to consult your doctor or a bone specialist.

I have read and understand the disclaimer

[Calculate Risk Factor](#) →

Figure 3. Garvan Fracture Risk Calculator online user interface

—About you—

Age (30-99):

Sex: Male Female

Ethnicity: ▼

—Clinical information—

Smoking status: ▼

Alcohol status: ▼

diabetes: ▼

Do either of your parents have osteoporosis/hip fracture?

Do you live in a nursing or care home?

Have you had a wrist spine hip or shoulder fracture?

History of falls?

Dementia?

Cancer?

Asthma or COPD?

Heart attack, angina, stroke or TIA

Chronic liver disease?

Chronic kidney disease (stage 4 or 5)?

Parkinson's disease?

Rheumatoid arthritis or SLE?

Malabsorption eg Crohn's disease, ulcerative colitis, coeliac disease, steatorrhea or blind loop syndrome?

Endocrine problems eg thyrotoxicosis, hyperparathyroidism, Cushing's syndrome?

Epilepsy or taking anticonvulsants?

Taking antidepressants?

Taking steroid tablets regularly?

Taking oestrogen only HRT?

—Leave blank if unknown—

—Body mass index—

Height (cm):

Weight (kg):

Calculate risk over ▼ years.

Figure 4. QFractureScores online user interface

Despite guidelines and assessment tools available for osteoporosis screening, there remains an osteoporosis care gap. Studies indicate that among men and women who are at high risk of fracture, only a minority actually receive treatment. In patients who sustain a fragility fracture, less than 20 percent received therapies to reduce the risk of fracture in the year following the fracture (L. Giangregorio, Papaioannou, Cranney, Zytaruk, & Adachi, 2006; John A. Kanis, Svedbom, Harvey, & McCloskey, 2014). In a prospective observational study of over 60,000 postmenopausal women aged 55 and older recruited from primary care practices in 10 countries, over 80 percent of women with a fragility fracture did not receive osteoporosis treatment (Greenspan et al., 2012). Furthermore, among patients that do initiate osteoporosis treatment, successful osteoporosis management is hindered by poor patient adherence to prescribed therapies (Brookhart et al., 2007; Gold & Silverman, 2006). Fracture liaison clinics have emerged as a potential solution to the osteoporosis care gap.

Fracture Liaison Services

Fracture Liaison Services (FLS), also referred to as Fracture Liaison Clinics, are secondary fracture prevention services implemented by health care systems for the treatment of osteoporotic patients. FLS operates by identifying patients presenting with fragility fractures, referring them for the necessary assessment of their bone health and fracture risk, and recommending or initiating appropriate treatment to prevent further fractures, especially more serious ones such as hip fractures.

One of the first FLS programs, implemented in 1999 across two Health Service Trusts in Glasgow, Scotland, reported notable improvements in identifying and evaluating patients with fractures (McLellan, Gallacher, Fraser, & McQuillan, 2003). The authors reported that within the first 18 months of FLS implementation, more than 4,600 fracture patients were identified and evaluated for osteoporosis, which represents almost all fractures estimated to occur in the population served by these two hospitals. Prior to implementation of the FLS, less than 10% of fracture patients were referred for osteoporosis evaluation. In the USA, the Kaiser Permanente Southern California (Kaiser SCAL) Healthy Bones FLS Program started in 2002 and reported a 37.2% reduction in hip fractures resulting in cost-savings of over \$30.8 million in the year 2006 alone (Dell, Greene, Schelkun, & Williams, 2008). Various FLS models have been implemented worldwide and have been shown to reduce the risk of future fractures and post-fracture mortality through efficiently identifying fracture patients, providing (BMD) and fracture risk assessment, increasing both the initiation and adherence of osteoporosis treatment,

providing ongoing monitoring and support, and providing fall prevention initiatives (Ganda et al., 2013; Chih-Hsing Wu et al., 2018).

The FLS models available today vary considerably in their structure and in the services they provide. FLS programs can range from inexpensive mail-based interventions that include telephone and print-based patient contacts, to physician notification and patient-specific reminders alongside printed treatment guidelines, to centralized coordination through an orthogeriatrician or nurse practitioner (C.-H. Wu et al., 2018).

There are a variety of ways to classify FLS programs including one method developed by researchers in Australia who classifies them into four categories (A-D) (Ganda et al., 2013). In this classification system, type A programs are the most comprehensive, utilizing the coordinator as the key player for the identification of patients, clinical investigation, and initiation of the appropriate osteoporosis treatment. Type B programs are similar, but the patient's primary care physician initiates the treatments instead of the FLS coordinator. In type C programs, patients are educated about the need for diagnosis, risk assessment, and possible treatment, and their primary care physicians are notified about the patient's fracture and the need for follow-up and risk assessment. In type D programs, patients receive only osteoporosis education and there is no outreach to the primary care physician. Type A and type B FLS models have the best outcomes and are more cost-effective (Ganda et al., 2013). Despite the different models, all FLS models have the unifying goal of identifying high-risk patients and referring them for appropriate treatment.

Specific Aims

The majority of fragility fracture patients evaluated by the FLS at Brigham and Women's Faulkner Hospital (BWHF) were patients with upper extremity fractures, predominantly proximal humerus and distal radius. History of an upper extremity fragility fracture is a risk factor for subsequent fractures, but it is not clear whether upper extremity fragility fracture patients are inherently at higher risk for future fractures compared to patients who have not experienced an upper extremity fracture, or whether the occurrence of fragility fracture is the primary difference between these two groups.

In this study, we compared the estimated FRAX 10-year probability of major osteoporotic fracture and hip fracture between two upper extremity patient cohorts: upper extremity fragility fracture patients over age 50 evaluated in the FLS clinic and similarly aged patients evaluated in the upper extremity clinic for non-fracture conditions. We hypothesized that upper extremity non-fracture patients would have lower FRAX risk for major osteoporotic and hip fractures compared to upper extremity fragility fracture patients. Our secondary goals were to assess whether these groups differed with respect to clinical demographics or rates of osteoporosis evaluation. In addition, we report the prevalence of BMD, PTH, and vitamin D lab abnormalities in upper extremity fragility fracture patients evaluated in our FLS.

METHODS

Participants

Institutional review board approval was obtained for this cross-sectional study. Patients referred to the Fracture Liaison Service (FLS) for osteoporosis evaluation following a fragility fracture, and patients evaluated in the upper extremity clinic for non-fracture upper extremity conditions were approached to fill out the study questionnaires.

Study Outcomes

Data was collected through two study questionnaires (see Appendix). Recruited participants were asked to complete the questionnaires following the completion of their appointments at the FLS or upper extremity clinic. The first questionnaire assessed fracture risk factors, fracture history, family history of fracture, osteoporosis treatment, supplementation, and dietary calcium intake from milk, yogurt, cheese, and calcium fortified orange juice. The second questionnaire assessed variables required to calculate a FRAX score. The primary outcome of this study was the 10-year probability of hip fracture and major osteoporotic fracture calculated by FRAX. Secondary study outcomes included estimated daily calcium intake, use of calcium and vitamin D supplementation, BMI, DXA history, fall history, smoking or alcohol use, prevalence of secondary osteoporosis, glucocorticoid use, DXA T scores, and use of osteoporosis medications (Fosamax (Alendronate), Boniva (Ibandronate), Aredia (Pamidronate), Actonel (Risedronate), Reclast (Zoledronate), estrogen hormone therapy, Evista (Raloxifene), Forteo (Teriparatide), and Prolia (Denosumab)). All data were collected via study

questionnaires with the exception of DXA T scores, which were collected via chart review. DXA results for spine, hip, femoral neck, and distal radius within one year of the FLS or hand clinic visit date were collected for analysis. Analyses of secondary study outcome data were conducted with the maximal available data collected (see Appendix).

FRAX Calculator

In this study, FRAX scores were calculated without BMDs since a limited number of upper extremity clinic patients had DXA scans. In addition, we calculated two FRAX scores for the FLS group: one including history of fragility fracture (FRAX Score-A) and one ignoring history of fragility fracture (FRAX Score-B). FRAX scores were calculated using the online tool, which can be found at <https://www.sheffield.ac.uk/FRAX/>.

Lab Abnormalities

The prevalence of abnormal DXA, high parathyroid hormone (PTH), and vitamin D deficiency was investigated for only patients evaluated in the FLS. Lab data were collected through chart review. Since very few patients obtained labs for PTH and vitamin D, lab results obtained within one year of the FLS visit date were included in our results. Similarly, BMD results from DXA obtained within two years of the FLS visit date were included in our results.

Statistical Analysis

Continuous variables were reported as means and assessed for normality before analysis with two-tailed Student's t tests. Nominal variables were analyzed using Fisher's exact tests. FRAX scores and estimated daily calcium intake were assessed for normality using Kolmogorov-Smirnov tests and were found to have lognormal distributions. Both continuous variables were log transformed before analysis with parametric unpaired t-tests and reported below as back transformed results. The primary analysis assessed both men and women in the analytic cohorts. In addition, a subanalysis of only women in the analytic cohorts was conducted.

A convenience sample was used. The standard significance criterion of $\alpha = 0.05$ and standard power criterion of $(1-\beta) = 0.80$ was employed for all statistical tests. The sample size of 243 (n=129 in the FLS group and 114 in the UE clinic group) affords > 80% power to detect a difference of 0.36 standard deviations between the two groups. Base upon the standard deviation of our FRAX-Score-A data, we will be able to detect a difference of 4.19 and 3.05 for hip fracture and major osteoporotic fracture respectively between the two groups. For a nominal variable with 10 percent prevalence, our sample size affords > 80% power to detect a relative risk of approximately 2.4 (i.e., 10% vs. 24%). For a variable with higher prevalence (25%), our sample size affords > 80% power to detect a relative risk of approximately 1.72 (i.e., 25% vs. 43%). All statistical analyses were conducted using GraphPad Prism and are reported as unadjusted results.

RESULTS

Subject Characteristics

During the study period, 219 patients aged 50 years old or over were seen in the FLS, and 175 similarly aged patients were seen in the upper extremity clinic. Patients evaluated in the FLS for non-upper extremity fragility fractures were excluded from the FLS analytic cohort. Patients who did not speak English or failed to complete the study questionnaires were also excluded from the analytic cohorts. Additionally, those who declined to report ethnicity and race were excluded, as these variables are required in order to calculate a FRAX score. After the exclusions, 129 and 114 patients made up the analytic cohort for the FLS and upper extremity groups respectively (**Figure 5**).

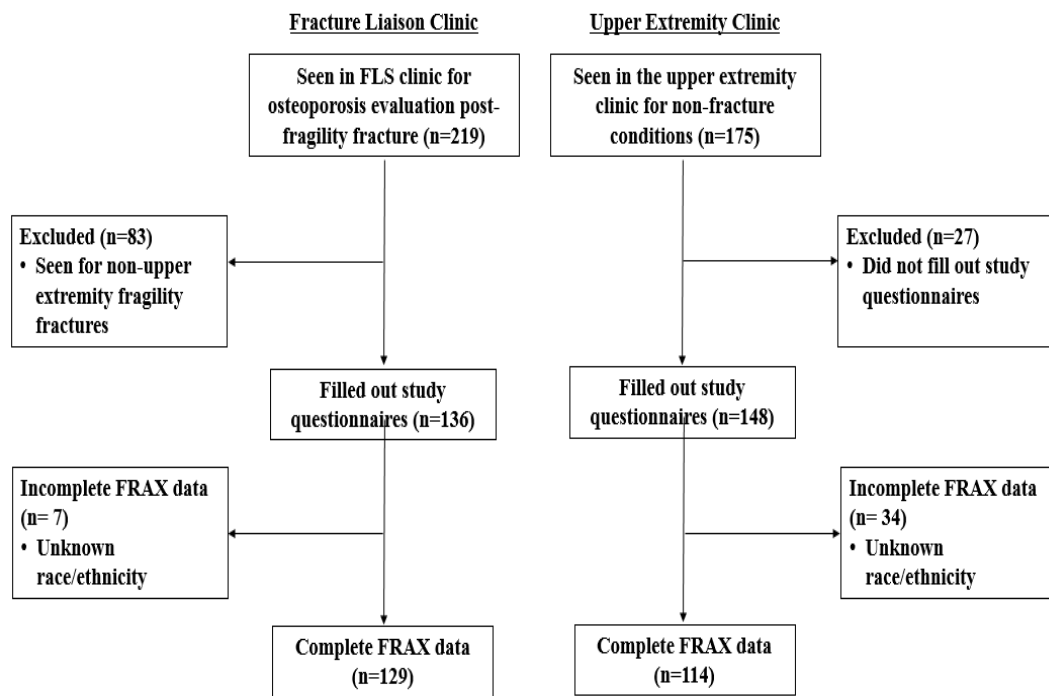


Figure 5. Selection of analytic cohorts

The analytic cohorts for the FLS and upper extremity group consisted of 129 and 114 subjects, respectively. Participants of this study were predominantly older white non-Hispanic females. The mean age, race and ethnicity distribution, and mean BMI were similar between the two groups (**Table 3**). The upper extremity group had significantly more males than the FLS group (26.42% versus 7.75%, $p = 0.0001$). Of the 129 UE fragility fracture patients evaluated in the FLS, 33 percent were proximal humerus fractures and 67 percent were distal radius fractures.

Table 3. Analytic cohort characteristics

	FLS (n = 129)	UE Clinic (n = 114)
Mean age (SD)	66.67 (9.80)	67.06 (9.79)
Gender (%)		
Female	92.25	73.68
Male	7.75	26.32
Race (%)		
Asian	1.55	0.88
Black or African American	1.55	4.39
Hispanic or Latino	4.65	0.00
White	92.25	94.74
Ethnicity (%)		
Hispanic	4.65	1.75
Non-Hispanic	95.35	98.25
Mean BMI (SD)	27.24 (5.34)	27.34 (6.47)

*SD = standard deviation; BMI = body mass index; FLS = fracture liaison service; UE = upper extremity

Lab Abnormalities

Of the 129 fragility fractures evaluated in the FLS, 66 percent and 57 percent had vitamin D and PTH lab tests within one year of their FLS visit date, respectively. Among the 85 FLS patients who had vitamin D labs, 16 percent were vitamin D deficient (defined as levels less than 20 ng/mL), 24 percent were vitamin D insufficient (defined as

levels between 20 and 30 ng/mL), and 60 percent were vitamin D sufficient (defined as levels greater than 30 ng/mL). Among the 74 FLS patients who had PTH labs, 9 percent had high PTH (defined as levels greater than 65 pg/mL). The average vitamin D and PTH levels among FLS patients were 35 ng/mL and 49 pg/mL, respectively.

FRAX Scores

The FRAX Score-A for major osteoporotic fracture was higher in the FLS group than the UE group (19.23 (17.58, 21.09) versus 9.23 (8.16, 10.45), $p < 0.001$). The FLS group also had a higher FRAX score for hip fracture (4.26 (3.60, 5.04) versus 1.54 (1.19, 1.99)), $p < 0.001$). However, when excluding history of fragility fracture in the FLS cohort (FRAX Score-B), there was no difference in FRAX scores for major osteoporotic fracture ($p = 0.095$) and hip fracture ($p = 0.215$). In a subanalysis of only women, similar results were observed (**Table 4**).

Table 4. FRAX Scores

	<u>Men and Women</u>			<u>Women Only</u>		
	FLS (n=129)	UE Clinic (n=114)	P Value	FLS (n=119)	UE Clinic (n= 84)	P Value
FRAX Score-A (95% CI)						
Major Osteoporotic	19.23 (17.58, 21.09)	9.23 (8.16, 10.45)	< 0.001	20.00 (18.24, 21.93)	10.14 (8.70, 11.80)	< 0.001
Hip	4.26 (3.60, 5.04)	1.54 (1.19, 1.99)	< 0.001	4.40 (3.69, 5.25)	1.69 (1.23, 2.31)	< 0.001
FRAX Score-B (95% CI)						
Major Osteoporotic	10.59 (9.52, 11.78)	9.23 (8.16, 10.45)	0.095	11.07 (9.92, 12.33)	10.14 (8.70, 11.80)	0.342
Hip	1.88 (1.54, 2.30)	1.54 (1.19, 1.99)	0.215	1.96 (1.59, 2.41)	1.69 (1.23, 2.31)	0.422

*CI = confidence interval; FLS = fracture liaison service; FRAX Score-A = FLS FRAX scores including history of fracture; FRAX Score-B = FLS FRAX scores excluding history of fracture; UE = upper extremity

*P values (two-sided) based on Student's t test

Fracture Risk Factors

Subjects in the FLS group were more likely to have secondary osteoporosis and glucocorticoids use. Secondary osteoporosis included type I insulin dependent diabetes, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, malabsorption, and chronic liver disease. Upper extremity subjects were more likely to have rheumatoid arthritis. There was no difference in smoking, alcohol use, parental hip fracture, and fall history within the past two years between the groups (**Table 5**). In a subanalysis of only women, similar results were observed with the exception of secondary osteoporosis, which was no longer statistically significant (see Appendix).

Table 5. Clinical risk factors

	FLS	UE Clinic	P Value
Currently smoking (%)			
Yes	6.62	2.03	0.076
No	93.38	97.97	
Alcohol intake > 3 units per day (%)			0.504
Yes	2.21	4.05	
No	97.79	95.95	
Parental hip fracture (%)			0.320
Yes	12.78	17.57	
No	87.22	82.43	
Rheumatoid Arthritis (%)			0.004
Yes	3.01	12.84	
No	96.99	87.16	
Glucocorticoid use (%)			0.004
Yes	16.30	5.41	
No	83.70	94.59	
Secondary Osteoporosis (%)			0.007
Yes	18.66	7.53	
No	81.34	92.47	
More than 2 falls in past year (%)			0.218

Yes	21.97	15.54
No	78.03	84.46

*FLS = fracture liaison service; UE = upper extremity

*Results include both men and women

*P values (two-sided) based on Fisher's exact test

Osteoporosis Evaluation and Treatment

Subjects in the FLS group were more likely to have had a DXA within the past 2 years and take calcium supplements (P values 0.0001 and 0.0005, respectively). There was no difference in vitamin D supplementation, osteoporosis medication use, or estimated daily dietary calcium intake between the two groups (**Table 6**). Subanalysis of only women showed that the prevalence of osteoporosis medication use was similar between FLS and upper extremity groups (P value = 0.8766, see Appendix).

Table 6. Osteoporosis Evaluation and Treatment

	FLS	UE Clinic	P Value
DXA within past 2 years (%)			< 0.001
Yes	93.02	37.16	
No	6.98	62.84	
Calcium supplementation (%)			0.001
Yes	58.72	42.86	
No	34.09	65.91	
Vitamin D supplementation (%)			0.790
Yes	66.07	63.97	
No	33.93	36.03	
Estimate daily Ca intake (95% CI)	796.16 mg (737.90, 859.01)	827.94 mg (755.09, 905.73)	0.515
Osteoporosis treatment (%)			0.079
Yes	47.06	34.88	
No	52.94	65.12	

*CI = confidence interval; DXA = dual-energy x-ray absorptiometry; FLS = fracture liaison service; UE = upper extremity

*Results include both men and women

*P value (two-sided) based on Fisher's exact test or Student's t test

DXA T Scores

Significantly more FLS subjects had DXA scans than upper extremity subjects. In the FLS group, 112, 114, 116, and 21 patients had DXA results for the spine, hip, femoral neck, and distal radius, respectively. In the upper extremity group, 28, 29, 28, and 9 patients had DXA results for the spine, hip, femoral neck, and distal radius, respectively. FLS subjects had a lower mean DXA T score in the distal radius when compared to upper extremity patients (**Table 7**). There was no difference in the mean DXA T score at the spine, femoral neck, and hip between groups (**Figure 6**). Of the FLS subjects who had DXA results, 42.4% and 50.4% of the patients had DXA T scores indicative of osteoporosis and osteopenia, respectively; 92.8% had abnormal DXA T scores. Of the upper extremity subjects who had DXA results, 35.5% and 48.4% of the subjects had DXA T scores indicative of osteoporosis and osteopenia, respectively; 83.9% had abnormal DXA results.

Table 7. Mean DXA T scores

	FLS	UE Clinic	P Value
Mean DXA T Score (95% CI)			
Spine	-1.433 (-1.662, -1.204)	-0.8857 (-1.582, -0.1897)	0.136
Hip	-1.326 (-1.501, -1.152)	-1.155 (-1.614, -0.6968)	0.412
Femoral neck	-1.943 (-2.100, -1.786)	-1.771 (-2.176, -1.367)	0.362
Distal radius	-2.410 (-3.145, -1.674)	-0.7556 (-2.013, 0.5017)	0.016

*CI = confidence interval; DXA = dual-energy x-ray absorptiometry; FLS = fracture liaison service; UE = upper extremity

*Results include both men and women

*P value (two-sided) based on Student's t test (parametric for spine, non-parametric for hip, femoral neck, and distal radius)

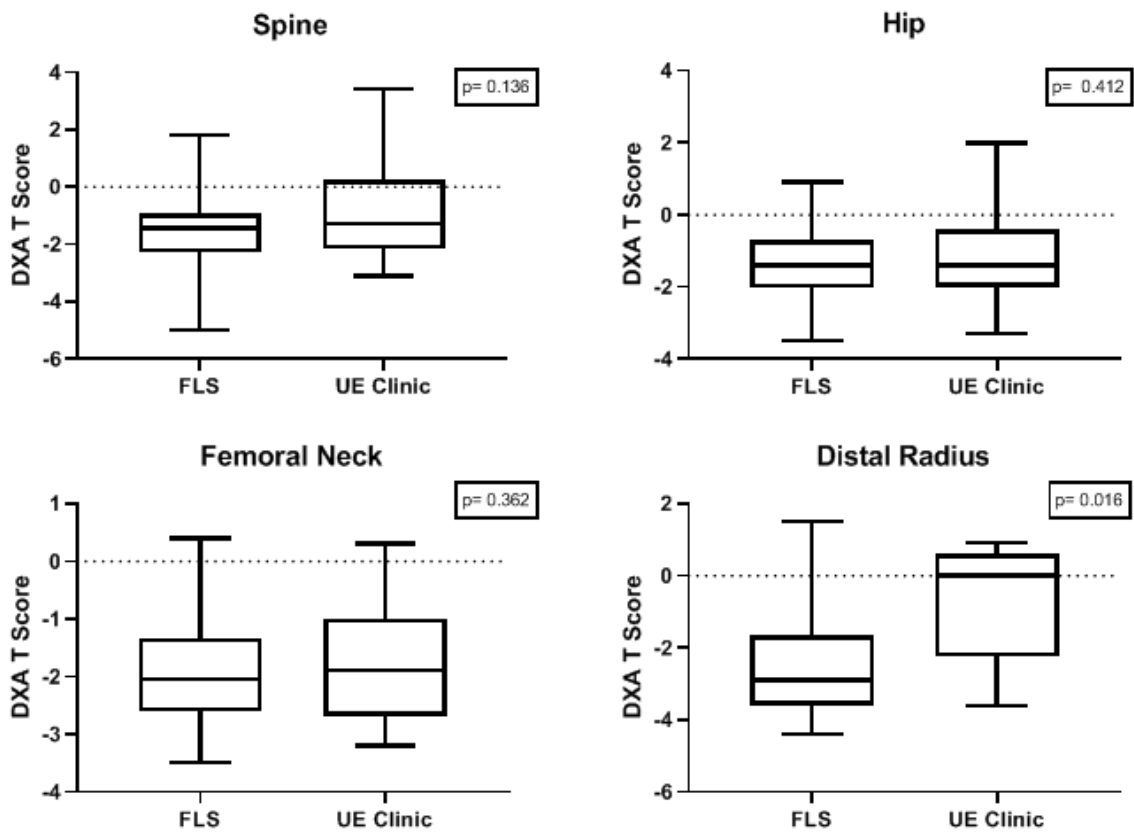


Figure 6. DXA T scores box and whisker plot

DISCUSSION

In this study, the estimated FRAX 10-year probability of major osteoporotic fracture and hip fracture between two upper extremity patient cohorts were compared: upper extremity fragility fracture subjects over age 50 evaluated in the FLS clinic and similarly aged subjects evaluated in the upper extremity clinic for non-fracture conditions.

The majority of subjects evaluated in the FLS and upper extremity (UE) clinic were older white non-Hispanic females. With respect to demographics and BMI, the UE fracture and UE non-fracture cohorts were similar, with the exception of more males in the UE non-fracture group. Low participation of men in FLS has been widely reported in the literature. A meta-analysis of over 25 FLS programs reported that women make up approximately 70.8 percent of all patients evaluated in FLSs (Ganda et al., 2013). The low percentage of men evaluated in FLSs suggests a potential greater osteoporosis care gap in men than women.

In this study, results showed that UE fracture subjects had an overall significantly higher 10-year probability of fracture at the hip, spine, forearm, and shoulder compared to UE non-fracture subjects. However, when excluding history of fragility fracture, UE fracture and UE non-fracture subjects had a similar 10-year probability for fracture. This result suggests that UE fracture and UE non-fracture patients, with the exception of fragility fracture history, harbor similar fracture clinical risk factors. Although, differences in the prevalence of glucocorticoid use, rheumatoid arthritis, and secondary

osteoporosis between the two groups was evident. In addition, these results highlight the importance of fragility fractures as a main driver in subsequent fracture risk. Indeed, patients who sustain a UE distal radial fragility fracture have twice the relative risk for future hip fracture (Freedman, Kaplan, Bilker, Strom, & Lowe, 2000).

In this study, UE fracture subjects on average had significantly lower BMD at the distal radius compared to UE non-fracture subjects, which was expected due to fragility fracture history among UE fracture subjects. UE fracture and UE non-fracture subjects had similar BMD T-scores at the spine, hip, and femoral neck. Among UE non-fracture subjects who had a DXA at any site, 35.5 percent and 48.4 percent of the DXA T scores were indicative of osteoporosis and osteopenia, respectively. Likewise, among UE fracture subjects who had a DXA at any site, 42.4 percent and 50.4 percent of the subjects had DXA T-scores indicative of osteoporosis and osteopenia, respectively. A total of 83.9 percent of available BMDs among UE non-fracture patients and 92.8 percent of available BMDs among UE fracture subjects were abnormal indicating an increased risk for fracture in these cohorts.

Studies have demonstrated that abnormal BMD, either osteoporotic or osteopenic, is associated with an increased risk of fracture (Leslie et al., 2007). Individuals with osteoporotic BMD, T-scores less than -2.5, have the highest risk of fracture. However, the absolute number of fractures is highest among individuals who have osteopenic BMD, in part since the prevalence of osteopenia is higher than prevalence of osteoporosis (Cranney, Jamal, Tsang, Josse, & Leslie, 2007; Schuit et al., 2004; Siris et al., 2004). In this study, a majority of the UE fracture and UE non-fracture subjects with DXA

screening had osteopenic BMD. It is important to mention that only a limited number of UE non-fracture subjects had a BMD assessment. Only 40 percent of UE non-fracture subjects had a DXA at any of the sites. The low number of BMD assessments among these subjects suggests that they are under-screened for osteoporosis despite harboring similar fracture clinical risk factors as UE fracture patients. In addition, the proportion of UE non-fracture subjects reported being on osteoporosis therapy was low. Interestingly, the proportion of UE fracture subjects on osteoporosis therapy was also low and no different than UE non-fracture subjects, despite having higher rates of DXA BMD screening and being at a higher risk for subsequent fracture.

Low rates of osteoporosis treatment initiation and adherence has been widely reported throughout the literature. It has been estimated that less than 20 percent of patients who sustain a fragility fracture actually start osteoporosis therapy within a year of their fracture (L. Giangregorio et al., 2006; John A. Kanis et al., 2014). Furthermore, among fragility fracture patients who do initiate osteoporosis therapy, very few are compliant enough with the therapy to optimally minimize their risk for subsequent fracture (Brookhart et al., 2007; Gold & Silverman, 2006).

Studies investigating the reasons for low osteoporosis treatment initiation and compliance report cost of therapy, patient reluctance, time and cost of diagnosing osteoporosis, side effects of osteoporosis medications, skepticism of osteoporosis medication effectiveness, lack of access to BMD screening, and a lack of time for physicians to address secondary prevention as barriers to successful therapy (Elliot-Gibson, Bogoch, Jamal, & Beaton, 2004). Furthermore, the media's coverage of rare but

serious side effects associated with bisphosphonate use, which include atypical femur fracture, osteonecrosis of the jaw, and esophageal cancer, has further exacerbated patients' reluctance to initiate and adhere to osteoporosis therapy, despite bisphosphonates' proven effectiveness to treat osteoporosis. With the risk of subsequent fractures increasing after sustaining a fragility fracture, the diagnosis and treatment of osteoporosis in patients with fragility fractures provides the opportunity to prevent future fractures. Since fractures are typically first treated by orthopedic surgeons in fracture clinics or emergency departments, orthopedic surgeons serve as an early point of contact for fragility fracture patients and are in a unique position to narrow the osteoporosis care gap. Therefore, efforts to improve osteoporosis evaluation and treatment among fragility fracture patients may best be directed toward orthopedic surgeons.

Initiatives have been taken to attempt to close the osteoporosis care gap. In 2012, the International Osteoporosis Foundation (IOF) launched The Capture the Fracture Campaign with the goal of facilitating adoption of FLS globally to reduce the incidence of secondary fractures throughout the world (Akesson et al., 2013). To help promote FLS implementation globally, The Capture the Fracture Campaign aims to develop mentoring programs, FLS implementation guidelines and toolkits, and grant programs for developing FLS systems. The campaign aims to guide development of FLS programs worldwide through the Best Practice Framework (BPF), which is a collection of internationally endorsed standards for best practices in secondary fracture prevention. The BPF is comprised of 13 standards, which serves as an international benchmark for FLS standards. FLSs are assigned a level of achievement depending on how successful

they are in each of the 13 standards. FLS programs that register with The IOF Capture the Fracture Campaign are assigned an overall rating (Unclassified, Bronze, Silver, or Gold) based on two criteria: care across four key fragility fracture patient groups (hip fracture, inpatient fractures, outpatient fracture, and vertebral fracture) and FLS organizational characteristics. In addition, IOF registered FLSs will be awarded IOF approval and a placement on the Capture the Fracture Campaign website's interactive map, which showcases each FLS to a global audience. In 2019, the total number of FLSs granted IOF approval grew to 225 from 35 different countries around the world, and this number is expected to grow. How effective these FLSs will be at reducing the osteoporosis care gap will need to be monitored.

The limitations of this study include a limited sample size, use of patient reported data, lack of lab data among patients evaluated in the UE clinic, limited lab and BMD data among patients evaluated in the FLS, exclusion of individuals who did not speak English, and limited demographic information. Additional demographics data including distance from the hospital and area deprivation index scores would have improved characterization of this study population. Additionally, the study population was comprised of predominantly white non-Hispanic females, which limits the generalizability of our findings. The limits of the FRAX tool as a predictor for future hip fracture and major osteoporotic fracture serves as another limitation. Limitations of FRAX include uncertainty regarding the range of error with fracture risk, lack of validation with BMD measurements by technologies other than DXA, lack of extensive validation in patients treated for fracture, and limitation to only four ethnicities

(Caucasian, Black, Hispanic, Asian) in the United States (Leib et al., 2011). In addition, FRAX may underestimate fracture probability in individuals with multiple fractures, high-dose glucocorticoid exposure (defined as doses of prednisone or its equivalent greater than 7.5mg/day), severe vertebral fractures, parental history of non-hip fragility fractures, and diabetes mellitus (L. M. Giangregorio et al., 2012; Leib et al., 2011).

In conclusion, history of fragility fracture is one of the main drivers for subsequent fracture risk. Our results indicate UE fracture and UE non-fracture patients share similar clinical risk factors for fracture. Closer osteoporosis evaluation for all older patients over 50 years old, including non-fracture patients, is warranted. Future studies should focus on addressing barriers to optimal osteoporosis management and the efficacy of implementation strategies designed to close the osteoporosis care gap.

APPENDIX

Table 8. Data completion status (Men and Women)

	FLS (n = 129)	UE Clinic (n = 114)
Complete FRAX variables	129 (100%)	114 (100%)
Estimate daily Ca intake	129 (100%)	107 (94%)
Vitamin D supplementation	107 (83%)	104 (91%)
Calcium supplementation	103 (79%)	104 (91%)
Currently smoking	129 (100%)	114 (100%)
Alcohol intake > 3 units per day	129 (100%)	114 (100%)
Parental hip fracture	129 (100%)	114 (100%)
Rheumatoid Arthritis	129 (100%)	114 (100%)
Glucocorticoid use	129 (100%)	114 (100%)
Secondary Osteoporosis	129 (100%)	113 (99%)
Activity level in past 12 months	129 (100%)	114 (100%)
DXA within past 2 years	125 (97%)	114 (100%)
Osteoporosis treatment	99 (77%)	101 (86%)

**The tables show number of data points available for each variable*

**To calculate a FRAX score, subjects must have an identifiable race and ethnicity; subjects who had race or ethnicity listed in EPIC as 'unknown', 'other', 'declined', or 'unavailable' were excluded from the analytic cohort*

Table 9. Data completion status (Women Only)

	FLS (n = 119)	UE Clinic (n = 84)
Complete FRAX**	119 (100%)	84 (100%)
Estimate daily Ca intake	119 (100%)	81 (96%)
Vitamin D supplementation	99 (83%)	84 (100%)
Calcium supplementation	95 (90%)	84 (100%)
Currently smoking	119 (100%)	84 (100%)
Alcohol intake > 3 units per day	119 (100%)	84 (100%)
Parental hip fracture	119 (100%)	84 (100%)
Rheumatoid Arthritis	119 (100%)	84 (100%)
Glucocorticoid use	119 (100%)	84 (100%)
Secondary Osteoporosis	119 (100%)	83 (99%)
Activity level in past 12 months	119 (100%)	84 (100%)
DXA within past 2 years	115 (97%)	84 (100%)
Osteoporosis treatment	90 (76%)	75 (89%)

**The tables show number of data points available for each variable*

**To calculate a FRAX score, subjects must have an identifiable race and ethnicity; subjects who had race or ethnicity listed in EPIC as 'unknown', 'other', 'declined', or 'unavailable' were excluded from the analytic cohort*

Table 10. Risk factors associated with fracture (Women Only)

	FLS	UE Clinic	P value
Currently smoking (%)			0.144
Yes	5.88	1.19	
No	94.12	98.81	
Alcohol intake > 3 units per day (%)			0.999
Yes	1.68	2.38	
No	98.32	97.62	
Parental hip fracture (%)			0.999
Yes	12.61	13.10	
No	87.39	86.90	
Rheumatoid Arthritis (%)			0.044
Yes	3.36	10.71	
No	96.64	89.29	
Glucocorticoid use (%)			0.002
Yes	17.65	3.57	
No	82.35	96.43	
Secondary Osteoporosis (%)			0.214
Yes	16.81	9.64	
No	83.19	90.36	
More than 2 falls in past year (%)			0.483
Yes	22.22	35.59	
No	77.78	43.13	

**FLS = fracture liaison service; UE = upper extremity*

**Results include both men and women*

**P values (two-sided) based on Fisher's exact test*

Table 11. Osteoporosis evaluation and treatment (Women Only)

	FLS	UE Clinic	P value
Estimate daily Ca intake (95% CI)	783.43mg (721.11, 851.14)	807.24 (711.21, 916.22)	0.683
Vitamin D supplementation (%)			0.635
Yes	66.67	70.24	
No	33.33	29.76	
Calcium supplementation (%)			0.053
Yes	61.05	46.43	
No	38.95	53.57	
DXA within past 2 years (%)			< 0.001
Yes	93.04	51.19	
No	6.96	48.81	
Osteoporosis treatment (%)			0.877
Yes	52.22	50.67	
No	47.78	49.33	

*CI = confidence interval; DXA = dual-energy x-ray absorptiometry; FLS = fracture liaison service; UE = upper extremity

*Results include both men and women

*P value (two-sided) based on Fisher's exact test or Student's t test

Table 12. Number of DXA T-scores available (Men and Women)

	FLS (n = 129)	UE Clinic (n = 114)
Spine	112 (87%)	28 (25%)
Hip	114 (88%)	29 (25%)
Femoral neck	116 (90%)	28 (25%)
Distal Radius	21 (16%)	9 (8%)

*FLS = fracture liaison service; UE = upper extremity

*Number of analytic cohort that has DXA results

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