Evaluation Of FRAX® score use in Maltese osteoporosis management guidelines

Mark R. Brincat, Raymond P. Galea, Eleanor Borg

Abstract

Objectives: Recent years have brought a shift towards evidence-based fracture risk engines. Fracture Risk Assessment Tool (FRAX®) is one such diagnostic tool used to evaluate the ten-year probability of osteoporotic fracture risk. The aim of this study was to evaluate the Maltese FRAX® score-based osteoporosis management guidelines and identify the suitability of using such a risk factor engine-based protocol.

Study design: Data from 702 patients presenting for bone mineral density (BMD) estimation in 2010-2011 were collected. In this period, local guidelines were devised but not yet put into practice so all referred patients underwent BMD estimation. These patients were below 65 years of age and above the minimum age for FRAX® use: 40 years. Data included Age, Weight, Height, BMI and the presence of any risk factor components of the FRAX® score tool. BMD was assessed using Norland/Hologic densitometers. FRAX® scores (excluding BMD) for each patient were calculated using the online tool www.shef.ac.uk/FRAX as accessed in 2014. The resulting major osteoporotic fracture risk was compared to age-specific assessment thresholds as set by Kanis et al. (2013). Thus the appropriateness (or otherwise) of densitometry measurements as dictated by local guidelines was determined.

Main outcome measures: The main outcome measures in this study were the femoral neck and vertebral body BMD. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of using the FRAX®-based guidelines in under 65 year olds were calculated.

Results: Local guidelines for managing <65 year olds were found to have a PPV of 11.26% and a NPV of 94.38 %

Conclusion: FRAX®-guided local guidelines are well suited at excluding non-osteoporotic patients (False omission rate of 5.62 %). Positive likelihood ratio for the protocol was found to be 1.27. This means that 1 in every 8.8 patients that would have been referred for BMD estimation were actually osteoporotic.

Keywords

Malta; Osteoporosis; Guidelines; Bone mineral density

Mark R. Brincat MD*
Basic Specialist Trainee in Obstetrics and Gynaecology
Mater Dei Hospital

Raymond P. Galea MD, FRCOG, Acc.Spec.O&G(Leuv), Ph.D.
Consultant Obstetrician and Gynaecologist
Mater Dei Hospital

Eleanor Borg MD
Foundation Doctor
Mater Dei Hospital

*Corresponding Author

Introduction

Due to increased longevity modern societies in developed countries face the exponential challenge of ageing populations. Consequently certain chronic medical conditions are becoming more frequent thus increasing the morbidity and mortality of the patients concerned. These chronic conditions are also consuming a bigger component of our health budgets.[1]

One of the problems associated with the aging process is a decrease in bone mass resulting in osteoporosis.[2] Osteoporosis has been defined as a multifactorial skeletal condition which is characterised by low bone mass and a deterioration of bone tissue leading to a deterioration of its macro and micro-architecture.[3] This results in increased bone fragility and consequently increased risk of fractures. It is termed to be a "*silent disease*", however, osteoporosis has potential serious implications on the functional status of the individuals concerned as well as the national health economy.[4]

The diagnosis of osteoporosis is dependent on the presence of either a fragility fracture or else on the bone density measurement. These fragility fractures can occur at any anatomical site although certain sites have been considered to be more characteristic than others. Vertebral fractures are the most common and even so, a significant proportion are clinically undiagnosed.[5] Hip fractures are associated with significant morbidity and mortality. About 50% of patients who lived independently before sustaining a hip fracture are unable regain their independent lifestyle.[6]

The World Health Organization (WHO) developed Bone Mineral Density (BMD) criteria for the diagnosis of osteoporosis from epidemiologic data that describe

the normal distribution of BMD in a young healthy reference population.[7-8] Osteoporosis is diagnosed when the BMD at the spine, hip, or wrist is 2.5 or more standard deviations (SD) below the reference mean. Low bone density or mass (sometimes referred to as osteopenia) is diagnosed when BMD is between 1.0–2.5 SD below the reference mean.

The number of standard deviation units above or below the young healthy mean is called the T-score. Another score used in the interpretation of BMD results is the Z-score which signifies the number of standard deviation units above or below the mean for the individual's own age group. Unfortunately BMD is only assessing one aspect of this condition and it does not cater for other factors such as bone quality and architecture which may play a significant role in fracture prediction.[9]

The epidemiology, pathophysiology and treatment of osteoporosis have greatly improved in the past decade and a change has been noted, from subjective case-specific strategies to risk engines that integrate all the risk factors, country-specific fracture rates and health-economic scenarios to offer country-specific intervention thresholds.

Various tools have been proposed so as to assess the patient's fracture risk by incorporating clinical risk factors with BMD. The World Health Organisation has developed one such tool which is based on individual patient models and incorporates the risks associated with clinical risk factors as well as BMD at the femoral neck. This tool is known as Fracture Risk Assessment Tool (FRAX®) and was developed at the World Health Organization Collaborating Centre for Metabolic Bone Diseases, in the University of Sheffield, UK.[10]

The algorithms used in FRAX® provide the 10-year probability of patients sustaining a fracture. The results are given as the 10-year probability of a fracture at the hip as well as at other sites such as spine, forearm, or shoulder (major osteoporotic fractures). The 10-year fracture probability is calculated from age, body mass index and dichotomized risk factors comprising prior fragility fracture (a fracture caused by injury that would be insufficient to fracture a normal bone), current tobacco smoking, use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and alcohol consumption.

The FRAX tool has been adopted at the Bone Density unit in Mater Dei Hospital in Malta. According to Maltese National Osteoporosis Management Guidelines women over 65 years of age with a FRAX® score (including BMD) above the intervention threshold are referred to the appropriate specialist for treatment. If FRAX® score (including BMD) lies below the intervention threshold, then the patient is re-assessed after two years. *(Figure 1)* Women under the age of 65 years who have a 10-year fracture probability as

obtained using FRAX® (excluding BMD) above the assessment threshold limits described below *(Table 1)* are referred for BMD assessment. If FRAX® (excluding BMD) 10-year fracture risk lies below the threshold the patient is reassured and reassesed after two years. *(Figure 2)* All patients with a history of previous fragility fracture are investigated and treated. The aim of this study was to assess the reliability of these guidelines and identify any particular positive or negative aspects of using such a risk factor engine-based protocol.

***Table 1**: Age-specific major osteoporotic fracture risk assessment thresholds as used in FRAX-score guided local guidelines*

Age	10-year Fracture probability (%)
40 – 44	2.3
45 - 49	2.4
50 – 54	2.9
54 - 59	3.6
60 - 64	4.9

Methods

Data for 702 patients that presented for official radiographic investigation of bone mineral density (BMD) estimation in 2010-2011 were collected. The data were collected during a period when local guidelines on management of osteoporosis were devised but not yet put into practice. Consequently, all referred patients underwent BMD estimation. It included age, indication for the test, weight, height and current medication. The presence of any of the risk factor components in the FRAX® score tool was also noted: previous fragility fracture, family history of hip fracture, tobacco use, alcohol consumption, glucocorticoid use, secondary causes of osteoporosis and confirmed rheumatoid arhritis. BMD (Lumbar and Femoral T-score) was assessed using Norland or Hologic densitometers and was noted on patients' data sheets. BMI was calculated following data entry.

FRAX® scores (without including BMD) for each patient were calculated using the online tool www.shef.ac.uk/FRAX® as accessed between July-October 2014. The resulting major osteoporotic fracture risk was compared to age-specific risk thresholds as set by Kanis et al. (2013). Thus the appropriateness (or otherwise) of densitometry measurements as dictated by local guidelines was determined.

Figure 1: Maltese Osteoporosis Management guidelines concerning over 65 year olds
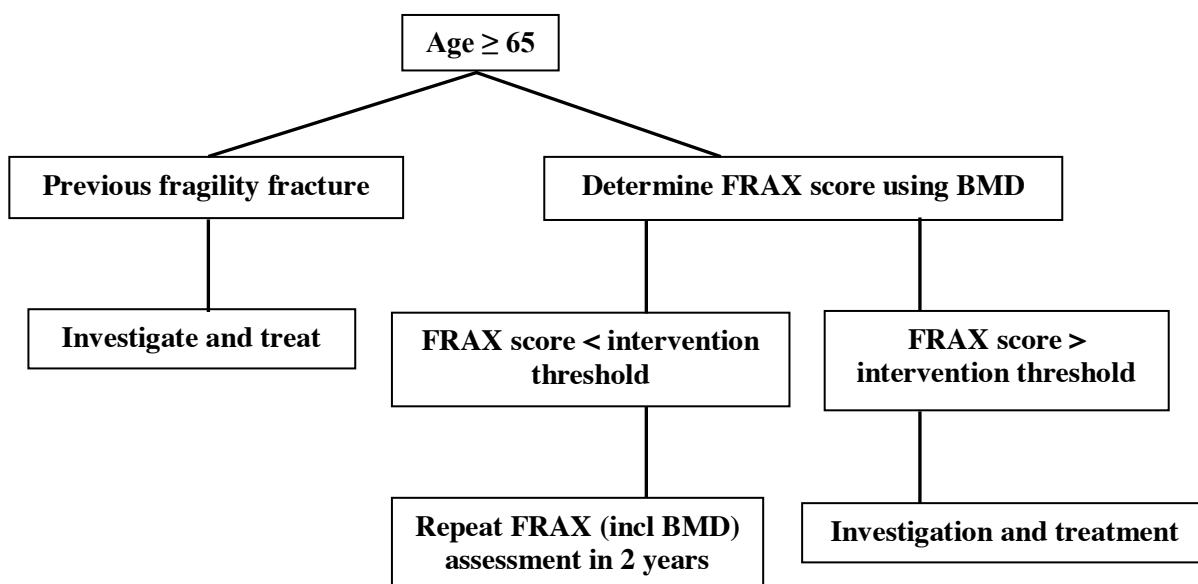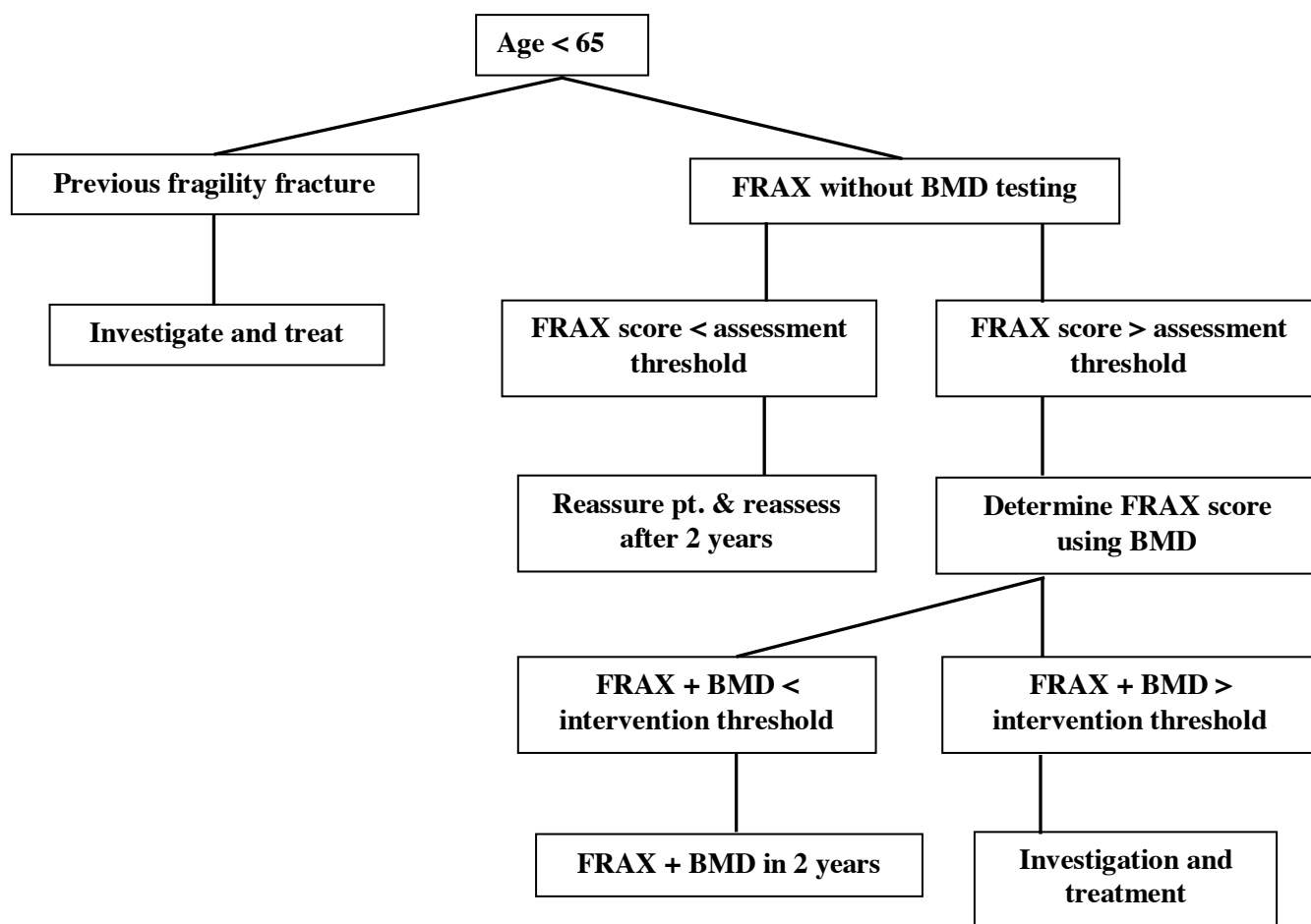
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                          ┌──────────────┐
                          │   Age ≥ 65   │
                          └──────┬───────┘
                   ┌─────────────┴──────────────┐
        ┌──────────────────────┐    ┌────────────────────────────┐
        │ Previous fragility    │    │ Determine FRAX score        │
        │ fracture              │    │ using BMD                   │
        └──────────┬───────────┘    └──────────┬─────────────────┘
                   │                 ┌──────────┴───────────┐
        ┌──────────────────┐ ┌────────────────────┐ ┌──────────────────────┐
        │ Investigate and  │ │ FRAX score <        │ │ FRAX score >          │
        │ treat            │ │ intervention        │ │ intervention threshold│
        └──────────────────┘ │ threshold           │ └──────────┬───────────┘
                             └──────────┬──────────┘            │
                          ┌─────────────────────────┐ ┌────────────────────────┐
                          │ Repeat FRAX (incl BMD)   │ │ Investigation and       │
                          │ assessment in 2 years    │ │ treatment               │
                          └─────────────────────────┘ └────────────────────────┘
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Figure 2: Maltese Osteoporosis Management guidelines concerning 40-64 year olds

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                          │  Age < 65    │
                          └──────┬───────┘
              ┌──────────────────┴──────────────────┐
     ┌──────────────────────┐           ┌──────────────────────────┐
     │ Previous fragility    │           │ FRAX without BMD testing  │
     │ fracture              │           └──────────┬───────────────┘
     └──────────┬───────────┘            ┌──────────┴───────────┐
     ┌──────────────────┐    ┌────────────────────┐ ┌──────────────────────┐
     │ Investigate and  │    │ FRAX score <        │ │ FRAX score >          │
     │ treat            │    │ assessment          │ │ assessment threshold  │
     └──────────────────┘    │ threshold           │ └──────────┬───────────┘
                             └──────────┬──────────┘            │
                          ┌─────────────────────────┐ ┌────────────────────────┐
                          │ Reassure pt. & reassess  │ │ Determine FRAX score    │
                          │ after 2 years            │ │ using BMD               │
                          └─────────────────────────┘ └──────────┬─────────────┘
                                               ┌─────────────────┴──────────────┐
                                    ┌──────────────────────┐ ┌──────────────────────┐
                                    │ FRAX + BMD <          │ │ FRAX + BMD >          │
                                    │ intervention threshold│ │ intervention threshold│
                                    └──────────┬───────────┘ └──────────┬───────────┘
                                    ┌──────────────────────┐ ┌──────────────────────┐
                                    │ FRAX + BMD in 2 years │ │ Investigation and     │
                                    └──────────────────────┘ │ treatment             │
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Results

Patient Data
Table 2: *Mean BMI, probability of major osteoporotic risk and hip fracture risk in the studied population*

AGE GROUP	POPULATION SIZE (N)	MEAN BMI	MEAN 10 YEAR PROBABILITY OF MAJOR OSTEOPOROTIC FRACTURE (FRAX)	MEAN 10 YEAR PROBABILITY OF HIP FRACTURE (FRAX)
40-44	5	26.4	2.28	0.2
45-49	40	27.7	2.82	0.255
50-54	184	28.1	3.29	0.38
55-59	226	27.9	4.62	0.74
60-64	247	28.6	6.78	1.45

Table of Sensitivity and Specificity
Table 3: *Sensitivity and specificity of using the local osteoporosis management guidelines according to age group*

AGE GROUP	40-44	45-49	50-54	55-59	60-64	OVERALL
TRUE POSITIVE	0	1	4	18	26	49
FALSE POSITIVE	1	27	83	124	151	386
TRUE NEGATIVE	4	11	92	79	66	252
FALSE NEGATIVE	0	1	5	5	4	15
SENSITIVITY	0%	50%	44.44%	78.26%	86.67%	76.56% 95% CI:64.3-86.2%
SPECIFICITY	80%	28.95%	52.57%	38.92%	30.41%	39.21% 95% CI:35.7-43.41%

FRAX[®](without BMD) based guideline use for managing under 65 year olds was found to have a positive predictive value of 11.26% (CI 8.45% to 14.62%) and a negative predictive value of 94.38% (CI 90.90% to 96.82%)

Sensitivity, specificity, positive predictive value and negative predictive value of using the FRAX[®] engine in under 65 year olds were calculated using true positive/negative and false positive/negative rates of each age group as described in local Maltese guidelines. The age groups under investigation were: 40-44, 45-49, 50-54, 55-59 and 60-64 year olds.

Discussion

From the data obtained it can be observed that FRAX[®]-guided local guidelines are well suited at excluding patients who are not osteoporotic. This can be seen from the high negative predictive value of 94.32% (with a false ommission rate of only 5.68%). If FRAX-guided local guidelines were strictly adhered to during this period, 252 bone density measurements (35.9% of all estimations) could have been avoided.

The likelihood ratios are used as part of evidence-based medicine to assess the value of carrying out a diagnostic test, in this case using the FRAX[®] score. The positive likelihood ratio for the protocol was found to be 1.27. This means that 1 in every 8.8 patients that would have been referred for BMD estimation would have actually been osteoporotic.

The protocol has a mean sensitivity of 76.56% across age groups, with the highest sensitivity being in the older age groups. This means that in these patients there is a higher probability that osteoporotics are correctly identified. The sensitivity of the local protocol investigated in this study is comparable to that obtained by Henry and colleagues in 2011.[11] This study prospectively evaluated the use of FRAX[®] in the United Kingdom (Sensitivity of 64.2%, Specificity of 62.9%) and in the United States (Sensitivity of 66.7%, Specificity of 59.7%). In a population of postmenopausal Thai women, Yingyuenyong and colleagues found FRAX[®] to have a sensitivity of 83.6% and a specificity of 72.1%.[12] The specificity of the protocol in the Maltese population (39.21%) is lower than that quoted in these studies. These observations may be due to dissimilarities in the assessment thresholds used, wherein increasing the sensitivity of a protocol (by lowering assessment thresholds) comes at the expense of decreasing the protocol's specificity. In this regard, a study by Bansal et al (2015) found lowering the assessment threshold from >9.3% major osteoporotic fracture risk (as recommended by the US preventative Services Task Force) to 5.5% resulted in a higher sensitivity (From 37 to 80%) and a lower specificity (From 74 to 27%).[13]

In agreement with other studies, linear regression analysis of Hip and Vertebral T-scores found them to be

in a significant negative relationship with age and in a positive relationship with BMI. This could be suggestive of a protective effect of obesity on bone density. In obese postmenopausal women, increased estrogen synthesis by fat tissue has been suggested as one of the potential mechanisms for the protective effect of fat mass on bone.[14]

A follow up assessment of the Maltese National Osteoporosis Management guidelines is planned in the coming years to assess the impact they will have on local practice and cost-effectiveness of bone mineral density estimation and to evaluate how these can be improved. A ten year follow up of the patients involved in this study is also planned in order to assess actual fracture incidence.

Conclusion

FRAX®-guided local guidelines are well suited at excluding non-osteoporotic patients, with a false omission rate of 5.62%. The sensitivity of the local protocol increases with increasing age, and its proper use in the Maltese community care could reduce load at the Bone Density units at Mater Dei Hospital.

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