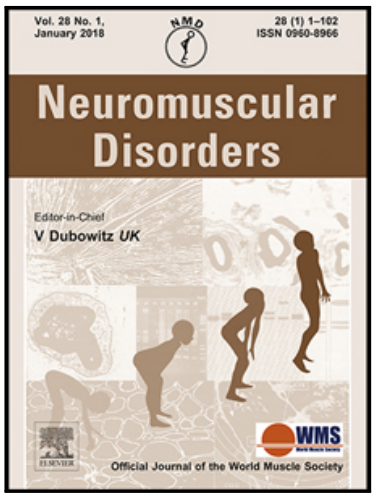


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# Fractures And Bone Health Monitoring In Boys With Duchenne Muscular Dystrophy Managed Within The Scottish Muscle Network

Shuko Joseph [1,2], Cunyi Wang [1, 3], Marina DiMarco [4], Iain Horrocks [2], Ishaq Abu-Arafeh [5], Alex Baxter [6], Nuno Cordeiro [7], Linda McLellan [8], Kenneth McWilliam [6], Karen Naismith [9], Elma Stephen [10], S. Faisal Ahmed [1], Sze Choong Wong [1]

[1]Developmental Endocrinology Research Group, Royal Hospital for Children, Glasgow,

[2]Paediatric Neurosciences Research Group, Royal Hospital for Children, Glasgow,

[3]School of Mathematics and Statistics, University of Glasgow,

[4]Scottish Muscle Network, Queen Elizabeth University Hospital, Glasgow,

[5]Department of Paediatrics, Forth Valley Royal Hospital, Stirlingshire,

[6]Department of Paediatric Neurology, Royal Hospital for Sick Children, Edinburgh,

[7]Department of Paediatrics, Crosshouse Hospital, Ayrshire,

[8]Department of Paediatrics, Raigmore Hospital, Inverness,

[9]Department of Paediatrics, Ninewells Hospital, Dundee,

[10]Department of Paediatrics, Royal Aberdeen Children's Hospital, Aberdeen,

United Kingdom

**Address for correspondence**

Dr. Sze Choong Wong,

Developmental Endocrinology Research Group, Royal Hospital for Children

1345 Govan Road, Glasgow G51 4TF United Kingdom

Tel: +44 141 451 5841

Email: jarod.wong@glasgow.ac.uk

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**Highlights**

- A high rate of radiologically confirmed symptomatic fractures (48%) was identified.
- Non-vertebral fractures occurred predominantly at femur and tibia after minor falls.
- DMD bone monitoring is currently inconsistent despite consensus guidance.

**Abstract**

There are limited reports of radiologically confirmed fractures and bone health monitoring in with Duchenne Muscular Dystrophy. We performed a retrospective study of 91 boys, with a median age of 11.0 years, who are currently managed in Scotland with the aim to assess the frequency of radiologically confirmed fractures and report on bone health monitoring in relation to International Care Consensus Guidance. Of these boys, 59 (65%) were receiving glucocorticoid (GC) therapy and 23 (25%) had received previous treatment. Of those currently on GC, 37 (63%) had an assessment of bone mineral density and none had routine imaging for vertebral fractures during the study period. Of the 91 boys, 44 (48%) had sustained at least one symptomatic radiographically confirmed fracture. The probability of sustaining a first symptomatic fracture was 50% by 12.8 years old (95%CI: 12.1, 13.6). The most common sites for non-vertebral fracture were the femur and tibia. In this review of boys with DMD, almost half had sustained at least one radiologically confirmed symptomatic fracture. There is a need for standardized bone health monitoring in DMD that includes routine imaging of the spine to identify vertebral fractures, given the persistence of insult to the skeleton in these boys.

**Introduction**

Duchenne Muscular Dystrophy is an X-linked recessive disorder occurring in 1 in 4000 live male births [1]. DMD is a life-limiting disorder associated with progressive muscle inflammation, degeneration, fatty infiltration and fibrosis leading to progressive motor disability. Most affected boys will be wheel chair dependent by the age of 12 years. Glucocorticoid (GC) therapy is the only disease-modifying option, which has been shown to improve short-term muscle function and strength [2] but other benefits including preservation

of upper limb function, reduction in risk of scoliosis and preservation of cardiac function are reported with prolonged use [3-5]. However, prolonged use of GC is associated with abnormalities of growth and skeletal development [6]. Due to the high fracture frequency, several international workshops have developed consensus on monitoring and management of bone health in DMD, including the need for vitamin D supplementation, regular monitoring of vitamin D levels and evaluation of bone mass with dual energy absorptiometry (DXA) [7-9]. Previous studies have shown that fractures may lead to premature loss of ambulation and may be associated with severe and life threatening complications like fat embolism syndrome [10].

Whilst it is recognized that fractures are common in these boys, it is difficult to be certain of the prevalence of fracture from published studies. Based on patient recall or case note review [11-17], fractures have been reported in over 40% of boys and young men. However, it is not clear from these reports if complete case ascertainment was achieved. In addition, most published studies are from a single site.

In Scotland, the care of boys with DMD is delivered locally in seven paediatric centres using nationally agreed standards within the framework of a national managed clinical network. All radiological imaging is available for sharing on a single national platform. The aim of this study was to utilize these opportunities and assess the occurrence of radiologically confirmed symptomatic fractures in boys and adolescents with DMD. In addition, a secondary aim of the study was to report on bone health monitoring in boys managed in Scotland.

**Methods**

A retrospective review of bone health of 91 boys with DMD currently managed in the 7 centres supported by the Scottish Muscle Network (SMN, www.smn.scot.nhs.uk) was performed as part of a service evaluation in December 2015. Cases were identified from a registry held by the SMN and cross-checked with the lead neuromuscular clinicians in the 7 centres in Scotland. Information on all cases from diagnosis to last clinic visit, closest to December 2015 were collected. The diagnosis of DMD was confirmed by DNA diagnostic

technique and/or confirmatory muscle biopsy.

Fractures were identified from the national radiological archive report (Picture Archiving and Communication System (PACS), GE Systems, Milwalkee, Wis) and classified into vertebral fracture (VF) and non-VF. X-rays were performed as clinically indicated due to symptoms of limb pain, back pain, documented injuries or swelling. Routine screening lateral thoracolumbar spine x-rays was not adopted as part of clinical care during the period of study. All X-rays were reported by a consultant radiologist at the local centre. Detailed characteristics of fractures were collected from case notes including mechanism of fracture and clinical characteristics at the time of fracture including age, GC regimen and duration, mobility status, vitamin D levels, dual energy x-ray absorptiometry (DXA). Non-ambulant status was defined by a continuous use of a wheelchair. DXA was performed for total body (TB) and lumbar spine (LS) bone mineral content (BMC) adjusted for bone area (BAr) as previously described, using Lunar Prodigy (GE Medical Systems, Waukesha, Wis., USA) [18]. Anthropometric measurements (height, body mass index) were converted into standard deviation score (SDS) using the 1990 UK growth reference data [19, 20]. Ambulant boys were measured by standing height whereas non-ambulant boys who had growth monitoring were measured by arm span.

*Statistics*

Statistical analysis was conducted using IBM SPSS Statistics Software Version 22 (SPSS Inc, Chicago). Results are reported as median ($25^{th}$ and $75^{th}$ centile). The effect of age and the duration of GC therapy on the probability of fractures was determined by Kaplan–Meier analysis in median (95% confidence interval). For the analysis of time to first fracture (VF and non-VF) against age and GC duration, censored cases were included. In addition, boys who discontinued GC were also included. A level of $p<0.05$ was used to denote statistical significance.

**Results**

*Population Characteristics*

Details of all 91 boys at last clinic visit are summarised in Table 1. The median age of the cohort was 11.3 years (7.8, 15.0). Of the 91, 46 (51%) were non-ambulant. Median height SDS at last clinic visit was available in 76 boys and was -1.4 (-2.7, -0.8). Of the 76, 19 (25%) had a height SDS < -2.0. Median BMI SDS was +1.6 (0.7, +2.2) with 13 (30%) having a BMI SDS > +2.0.

*Glucocorticoid therapy*

Of the 91, 59 (65%) were on GC therapy at last clinic visit and 23 (25%) were previously treated with GC. Median length of GC in the boys who were previously treated was 4.2 years (2.8, 6.6). Of the 23 who were previously treated with GC, 17 discontinued at the time of loss of ambulation at a median age of 10.2 years (9.0, 11.5). Five discontinued after loss of ambulation due to excessive weight gain and 1 discontinued due to severe behavioural issues whilst still ambulant at 9.6 years of age. There were four different GC regimens used [Table 1]. Of the 59 on GC, 23 (40%) were treated with daily Deflazacort and only one boy was managed on pulsed Deflazacort. GC regimen was unknown for six who were enrolled in a randomized trial with the aim to evaluate the optimal GC regimen in DMD. All six were however treated with GC. Of the 32 who were not currently on GC, 9 were younger GC naïve boys (≤ 5 years). Median hydrocortisone equivalent was highest in daily Deflazacort, followed by daily Prednisolone and pulsed Prednisolone regimen at a median dose of 94.0 mg/m$^2$/day (45.0, 138.0), 69.5 mg/m$^2$/day (64.8, 75.8), 31.0 mg/m$^2$/day (13.5, 37.0), respectively.

*Bone health monitoring*

Of the 91, 46 (51%) had plasma 25 hydroxy-vitamin D levels measured in the last 12 months. Median vitamin D level was 49 nmol/L (23, 143). Of the 91, 63 (69%) had at least one DXA assessment. Of the 28 who have never had any DXA assessment, 8 (29%) were GC naïve boys ≤ 5 years. Of the 59 currently on GC, 37 (63%) had a DXA assessment in the

last 2 years.

*Vitamin D therapy*

Of the 91, 69 (76%) were on vitamin D supplementation. Of the 59 currently on GC, 48 (81%) were on vitamin D supplementation. Median vitamin D dose was 800 IU daily (400, 1400).

*Bisphosphonate therapy*

Of the 91, 10 (11%) were receiving bisphosphonate therapy. Of the 10, 8 (80%) were receiving intravenous bisphosphonate therapy, of whom six were on zoledronate, and two on pamidronate. The indications for treatment were symptomatic VFs in 7 boys and multiple long bone fractures in another boy. The remaining two boys (20%) were receiving oral risedronate. One was commenced after a long bone fracture, and the other was started as prophylaxis, however, subsequently developed femoral fracture on treatment. Two other boys were previously treated with bisphosphonate. Of these, one boy received a single dose of pamidronate for back pain with low LS bone mineral density SDS -2.5 without evidence of VF on X-ray. The other boy completed two years of 4 monthly pamidronate for symptomatic VF.

*Testosterone therapy*

Of the 91, 29 (32%) were 14 years or older and of this group, pubertal assessment was only documented in 14 (48%), all following referral to paediatric endocrinologist as a result of parental or clinician concern about delayed puberty. Of the 29, 11 (79%) were prepubertal with testes volume of less than 4 ml. Of these 11 boys, five were on intramuscular testosterone and two on oral testosterone for pubertal induction. None had received growth hormone therapy.

*Fracture occurrence*

Of the 91, 44 (48%) sustained a total of 51 fractures. Of the 91, 36 (40%) had non-VFs, 7 had symptomatic VFs (8%) and 1 had both non-VFs and symptomatic VFs. Of the 44, 5 (11%) sustained multiple fractures. The number of fractures sustained per individual ranged from 1 to 4. There were 43 non-VF episodes and these occurred predominantly in the lower limb in 31 (72%) [Figure 1] with the most common site being the femur in 14 (33%) followed by tibia in 12 (30%). Of the 43 non-VF episodes, 36 (84%) were fragility fractures [21] with 26 (61%) occurring after a fall from a standing position and 10 (23%) occurring in non-ambulant boys following a fall from a sitting position. In 6 (14%), non-VFs occurred following a history of minor trauma and in 1 boy mechanism of injury was not documented. All the 8 boys with symptomatic VFs presented with multiple painful VFs. The location of fractures included multiple thoracic and lumbar in 6, multiple lumbar in 1 and multiple thoracic in 1. A boy sustained three long bone fractures before the diagnosis of symptomatic VF. The first fracture was fracture of the tibia aged 2.1 years due to a fall from standing, prior to treatment with GC.

Of the 36 boys who sustained non-VFs, 20 (56%) were ambulant prior to the fracture and 7 (35%) never regained ambulation following the fracture. 6 out of the 8 (75%) boys were ambulant at the time that symptomatic VFs were diagnosed. None of the boys lost ambulation following diagnosis of symptomatic VF.

*Age and fracture*

The probability of developing a first symptomatic fracture (non-VF or symptomatic VF) was 50% by 12.8 years old (95%CI 12.1 to 13.6) [Figure 2a]. The probability of developing non-VF was 50% by 13.6 years old (95% CI 12.3 to 14.8). Non-VFs occurred over a wide age range of 2.0 to 17.4 years. The probability of developing symptomatic VF was 50% at 11.4 years old (95% CI 10.0 to 12.4). Symptomatic VFs occurred over an age range of 5.6 to 15.9 years.

*GC duration and fracture*

The probability of developing a first symptomatic fracture (non-VF or symptomatic VF) was 50% after 6.5 years of GC exposure (95% CI 5.4 to 7.5) [Fig. 2b]. The probability of developing non-VF was 50% after 8.2 years of GC exposure (95% CI 6.2 to 10.2). Seven non-VFs occurred in 26 ambulant GC-naïve boys with a median age at fracture of 3.5 years (2.0, 10.1). In contrast, symptomatic VFs only occurred in the GC-treated cohort. There was a latency of 2.3 years before the development of the first symptomatic VF. The probability of developing symptomatic VF was 50% at 3.7 years of GC exposure (95% CI 2.8 to 5.3).

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*Vitamin D, DXA and fracture*

Of the 51 fracture events, 33 (65%) had 25 hydroxy-vitamin D measured at the time of fracture. Median 25 hydroxy-vitamin D concentration at time of fracture was 49 nmol/L (24, 69). Of the 33, 3 (9%) had measurements <25 nmol/L. Of the 47 who did not sustain any fractures, median 25 hydroxy-vitamin D at last visit was 49 nmol/L (20,125).

Of the 51 fracture events, DXA TB BMC SDS and LS BMC SDS within six months of fracture were available in 18 (35%) and 17 (33%), respectively. Of the 13 with non-VFs who had a DXA within 6 months of the fracture, only one had TB BMC SDS < -2.0. Of the 5 with VFs who had a DXA within 6 months of the fracture, similarly only one had TB BMC SDS and LS BMC SDS < -2.

**Discussion**

This study of a contemporary group of boys with DMD managed in Scotland showed that almost half of the group had sustained at least one fracture and almost 9% of boys had presented with severe painful VFs. The mechanisms of injury suggest that 84% of non-VFs in our DMD boys were classified as fragility fractures, occurring following a fall from standing height or less[21]. Our study also showed that bone monitoring in Scotland according to current international consensus remains inconsistent, although it is unclear if this is an issue in other regions [7-9]. Only half of the cohort had vitamin D levels measured in the previous twelve months and only approximately 60% of GC treated boys had a DXA scan in the previous two years.

When compared to the prevalence of fracture of 9% reported in a large cohort of healthy children in the United Kingdom, the prevalence of fracture in DMD in the current study (48%) is clearly much higher [22]. In healthy children, upper limb long bone fractures at radius and ulna are the most common sites. In contrast, the two most common sites of fractures in the current cohort are femur and tibia [22]. A previous study has reported that lower limb fractures are the most common non-VFs but to the best of our knowledge detailed information on fracture sites in DMD have not been reported [23]. Compared to published studies of fractures in DMD, the frequency of non-VFs of 40% in the current study appears to be higher than the reported frequency of 23-30%, although a recent study has also reported similar frequencies of non-VF [24]. We believe that the frequency of non-VF in the current study is robust given that we included cases that were radiologically confirmed.

The prevalence of VFs of almost 9% in the current study is much lower than the reported 18-76% in published literature in DMD [15-17, 23-27]. Several factors could explain the differences in fracture occurrence including number of cases, GC regimen and dose, duration of treatment/follow-up and method of VF identification. Ten percent of the study cohort was also GC naïve. In recent studies, VF was detected in 53-76% in groups of boys on daily GC for at least three years when routine spine imaging was incorporated as part of bone health monitoring [24, 25]. During the study period, none of the Scottish centres included routine spine imaging for VF. We believe that the frequency of almost 9% of VF presenting with significant pain in our cohort represents a gross underestimation in these boys. It is now well recognized that VF in children with chronic conditions are often asymptomatic [26-28]. Since 2016, we have revised the bone monitoring guidance of the Scottish Muscle Network, to incorporate routine thoracolumbar spine x-rays (at least every 2 years) to detect VF [24].

The frequency of VF up to 16% is reported at diagnosis in other groups of children with treated with GC where systematic screening with spine x-rays was conducted [28-30]. In childhood leukaemia, where intermittent GC is used, almost a quarter developed VF over a period of four years when a routine screening programme with spine x-rays was in place[30]. Vertebral reshaping is possible in some children with leukaemia or other children with

chronic conditions who develop VF during shorter duration of GC therapy [6, 31,33, 34]. On the other hand, results from a retrospective study suggest that there is absent vertebral reshaping after diagnosis of VF in DMD which may be due to the prolonged period of GC therapy and irreversibility of the skeletal insult[24]. In our current review, we identified that delayed puberty is very common and present in almost 80% of older adolescents who have had clinical assessment of puberty following referral to paediatric endocrinology[35]. However, puberty was only documented in half the cohort of boys age 14 years and older. The prevalence of delayed puberty in these GC treated boys is therefore currently still unknown. Testosterone leads to increased bone mass by increasing periosteal expansion [36-38] and pubertal delay will no doubt contribute in part to poor bone development in these adolescents. Emerging evidence suggests that these boys have persistent hypogonadism, and may therefore have long-term consequences to the skeleton even in adulthood[39]. There are limited studies on the effects of testosterone on skeletal development and growth in boys with DMD but this deserves greater attention [39]. The importance of assessment and management of delayed puberty in these boys is addressed in our updated bone monitoring guidance, which recommends routine pubertal assessment from the age of 13 years, ideally by a paediatric endocrinologist. Management of puberty with testosterone from the age of 14 years building up to adult doses over a period of 2 to 3 years is currently our clinical practice.

It is worth noting that the median age of loss of ambulation in our national cohort of boys with DMD appears to be younger than those reported in some recent literature [40]. In contrast to a recent report [16], we did not find increased fracture incidence around the time of loss of ambulation, even though the age at loss of ambulation in our national cohort appears to be similar to that study and also other reports [41]. Some of the other published studies reporting a much later age of loss of ambulation are either from relatively small cohorts or did not include censored cases, thereby creating a bias of excluding those cases with a more severe phenotype or less responsive to GC [23,42,43]. The number of subjects in this study poses limitation in applying multivariable analysis to explore the influence of covariates on fracture risk. For example, the influence of different GC regimens, bisphosphonates,

testosterone therapies, pubertal status, vitamin D levels and bone mineral density will require exploration in a larger cohort. The complex interplay between underlying muscle weakness and GC therapy, together with other factors that may impact on bone health and therefore fracture risk in DMD needs to be teased out in well-designed research studies. Routine imaging with lateral thoracolumbar spine x-rays should be incorporated into such studies, and indeed in clinical monitoring of these boys[44].

## Conclusion

In summary, in one of the largest studies to date with complete ascertainment of boys with DMD, the current study reports a very high rate of radiologically confirmed fractures. The frequency of VF in our study is however likely to be a gross underestimation of the real frequency in this population. Bone monitoring in this national cohort is inconsistent and should now include routine imaging of the spine with lateral thoracolumbar spine x-rays. Routine pubertal assessment in these boys should be given attention in the neuromuscular clinics with timely referral to paediatric endocrinology for management of puberty. Multi-centre prospective studies are required to clearly understand the determinants of asymptomatic as well as symptomatic fractures in this at-risk group.

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## Disclosure Statement

The authors have no conflict of interest to disclose.

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**Legend to figures**

**Figure 1: Anatomical location of non-VFs in boys with DMD.**

Of the 91 boys, 37 developed non-VF (including 1 boy with non-VF and VF). The 37 boys sustained a total of 43 non-VFs.

[VF: vertebral fracture; DMD: Duchenne muscular dystrophy].

**Figure 2: Probability of fracture in boys with DMD against age and duration of GC exposure**

Horizontal dotted line refers to 50% probability of fracture (Fig a, and b). Vertical continuous line refers to mean age of loss of ambulation of boys with DMD in our cohort (Fig a). Vertical dotted lines refers to ± 1 standard deviation from the mean of age of loss of ambulation (Fig a).

[DMD: Duchenne muscular dystrophy; VF: vertebral fracture; GC: glucocorticoid]

(a) Probability of first symptomatic fracture in DMD over time (against age) using Kaplan-Meier analysis

The probability of developing first symptomatic fracture (symptomatic VF and non-VF) was 50% by 12.8 years of age. (Censored cases are shown as the crosses on Kaplan-Meier graph). Cases with previous GC treatment were also included.

(b) Probability of first symptomatic fracture in DMD in relation to duration of GC exposure using Kaplan-Meier analysis

The probability of developing first symptomatic fracture (symptomatic VF and non-VF) was 50% after 6.5 years of GC exposure. (Censored cases

are shown as the crosses on Kaplan-Meier graph). Cases with previous GC treatment were also included.

| | n (%) | Median ($25^{th}$, $75^{th}$ centile) |
|---|---|---|
| **Age (years)** | 91/91(100%) | 11.0 (7.8, 15.0) |
| **Height SDS** | 76/91 (84%) | -1.4 (-2.7, -0.8) |
| **BMI SDS** | 76/91 (84%) | +1.5 (0.7, 2.2) |
| **Non-ambulant cohort** | 46/91 (51%) | |
| **Age at loss of ambulation (years)** | 46/46 (100%) | 10.2 (8.8,11.7) |
| **Length of non-ambulation state (years)** | 46/46 (100%) | 2.9 (1.5, 6.0) |
| **Current GC treatment** | 59/91 (65%) | |
| **Previous GC treatment** | 23/91 (25%) | |
| **GC naïve** | 9/91 (10%) | |
| **Age at start of GC (years)** | 82/82 (100%) | 5.5 (4.4, 6.6) |
| **Duration of GC therapy (years)** | 82/82 (100%) | 5.2 (2.4, 8.0) |
| **Hydrocortisone equivalent dose (mg/$m^2$/day)** | | |
| **-Daily deflazacort** | 23/59 (40%) | 94.0 (45,138) |
| **-Daily prednisolone** | 16/59 (27%) | 69.5 (64.8, 75.8) |
| **-Pulsed prednisolone** | 13/59 (22%) | 31.0 (13.5,37.0) |
| **-Pulsed deflazacort** | 1/59 (2%) | 66.0 |
| **-Unknown GC regimen (Clinical Trial)** | 6/59 (10%) | |

**Table 1: Clinical characteristics of boys with DMD in Scotland at last clinic visit**

SDS: standard deviation score; BMI: body mass index; GC: glucocorticoid; mg: milligram; $m^2$: meter square; DMD: Duchenne muscular dystrophy

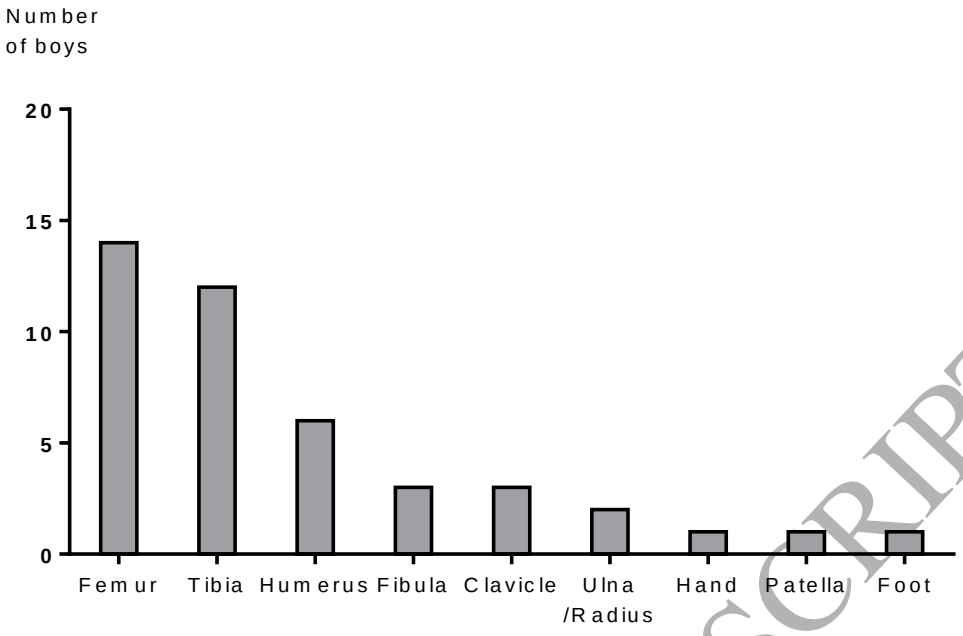


**Figure 1**

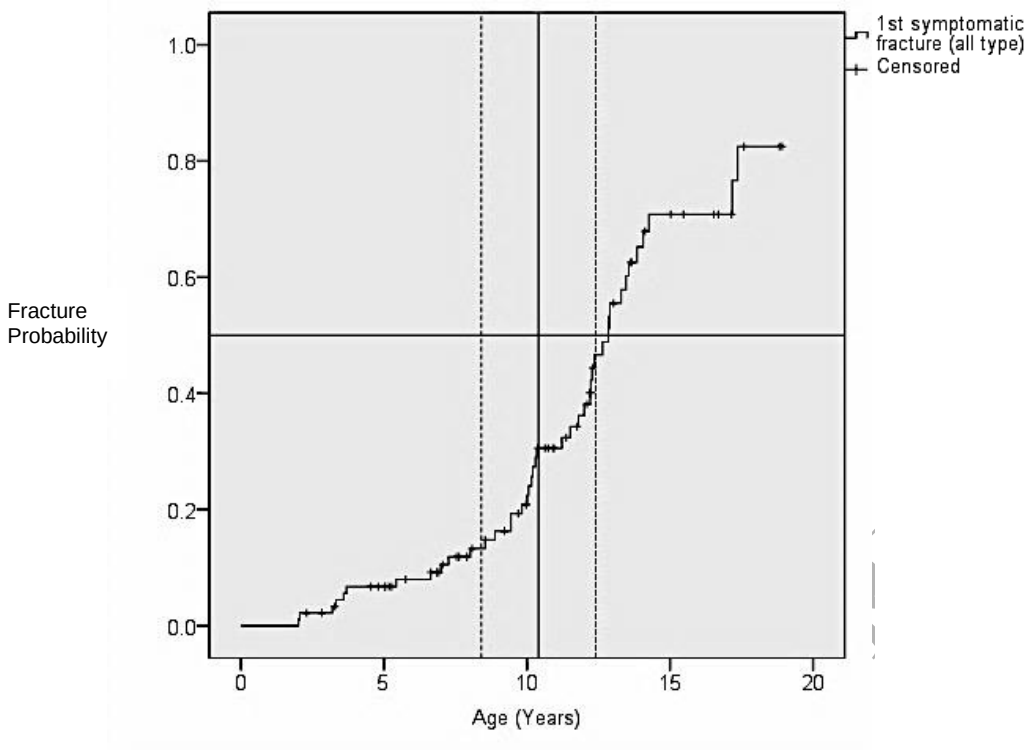


**Figure 2(a)**

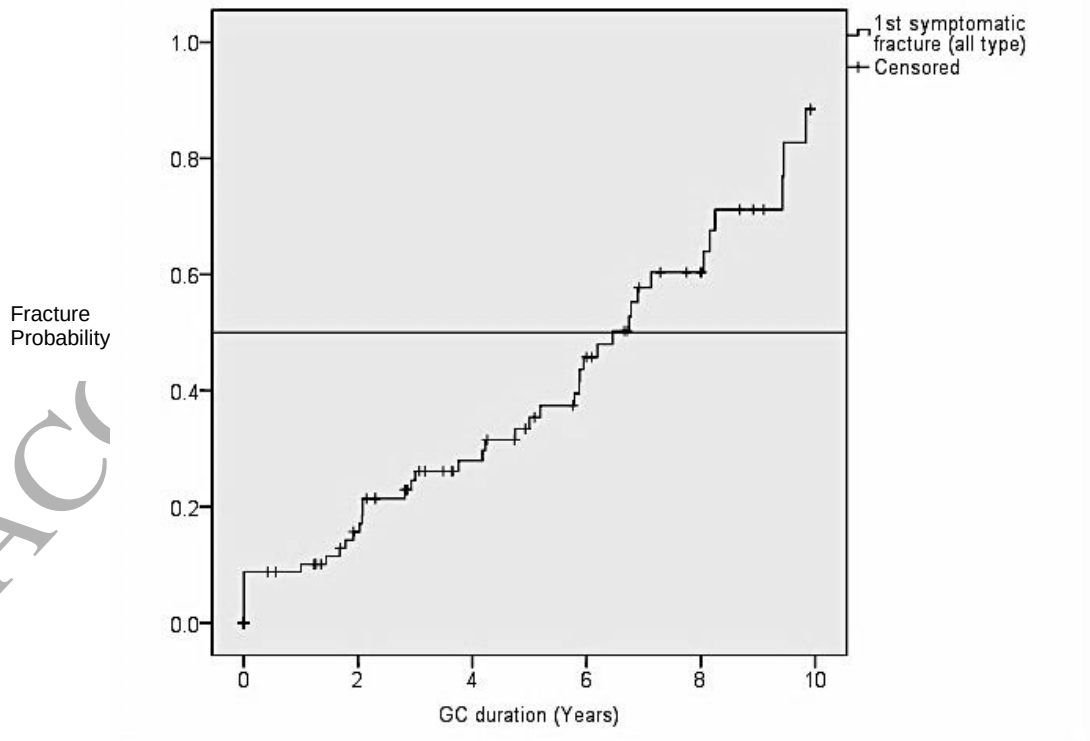


**Figure 2(b)**