Mirels' Score for upper limb metastatic lesions: Do we need a different cut-off for recommending prophylactic fixation?

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Title Page

Title

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Running Title

Validity of Mirels' Score in Upper Limb Metastasis.

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Mirels's Score for upper limb metastatic lesions: Do we need a different cut-off for recommending prophylactic fixation?

Abstract

The aim of this study was to investigate the reproducibility, reliability and accuracy of Mirels's score in upper limb bony metastatic disease and validate its use in predicting pathological fractures.

Methods

45 patients with upper limb bony metastases met the inclusion criteria (62% male 28/45). Mean age was 69 years (SD 9.5) and commonest primaries were lung (29% 13/45), followed by prostate and hematological (each 20% 9/45). The most commonly affected bone was the humerus (76% 35/45), followed by the ulna (6.5% 3/45). Mirels's score was calculated in 32 patients; with plain radiographs at index presentation scored using Mirels's system by 6 raters. The radiological aspects (lesion size and appearance) were scored twice by each rater (2-weeks apart). Intra- and interobserver reliability were calculated using Fleiss' kappa test. Bland-Altman plots compared the variances of both individual components and total Mirels's score.

Results

The overall fracture rate of upper limb metastatic lesions was 76% (35/46) with a mean follow-up of 3.6 years (range 11 months-6.8 years). Where time from diagnosis to fracture was known (n=20), fractures occurred at a median 19 days (IQR 60-10) and 80% (16/20) occurred within 3-months of diagnosis.

Mirels's score of ≥9 did not accurately predict lesions that fractured (fracture rate 11% 5/46 for Mirels's ≥9 versus 65% 30/46 for Mirels's ≤8, $p<0.001$). Sensitivity was 14% and specificity was 73%. When Mirels's cut-off was lowered to ≥7, patients were more likely to

fracture than not (48% 22/46 versus 28% 13/46, p=0.045), sensitivity rose to 63% but specificity fell to 55%.

Kappa values for interobserver variability were k=0.358 (fair, 95% confidence interval CI 0.288-0.429) for lesion size, k=0.107 (poor, 95% CI 0.02-0.193) for radiological appearance and k=0.274 (fair, 95% CI 0.229-0.318) for total Mirels's score. Values for intraobserver variability were k=0.716 (good, 95% CI 0.432-0.999) for lesion size, k=0.427 (moderate, 95% CI 0.195-0.768) for radiological appearance and 0.580 (moderate, 95% CI 0.395-0.765) for total Mirels's score.

Conclusions

This study demonstrates moderate to substantial agreement between and within raters using Mirels's score on upper limb radiographs. However, Mirels's score had a poor sensitivity and specificity in predicting upper extremity fractures. Until a more valid scoring system has been developed, based on our study, we recommend a Mirels's threshold of ≥7/12 for considering prophylactic fixation of impending upper limb pathological fractures. This contrasts with the current ≥9/12 cut-off, which is recommended for lower limb pathological fractures.

Keywords

Mirels's score; upper limb; metastasis; validity; reproducibility.

Level of evidence: Basic Science Study; Validation of Classification System

The most common cause of destructive bone lesions in the adult population is metastatic bone disease (MBD) with the humerus the second most frequently involved long bone[8,12]. Pathological fractures occur in up to 10% of patients with bony metastases and are associated with pain, metabolic disturbance and a negative impact on quality of life[4]. In addition, presence of a metastatic fracture is a negative prognostic factor and is associated with

increased mortality[7,20]. Accurate prediction of those with bony lesions likely to sustain metastatic fractures could minimize the need for treatment, improve patient outcomes and make subsequent surgery technically easier[16,20,22].

Mirels's score, devised in 1989, provides a composite weighted scoring system (from 4 to 12) to predict the likelihood of sustaining a pathological fracture based on pain, anatomical site, lesion size and radiographic appearance (Figure 1)[19]. Mirels's looked retrospectively at 38 patients with 78 long bone metastases (classified by region as non-weight-bearing bone, weight-bearing bone or per-trochanteric), with scores ≥8 recommending a 15% fracture risk and ≥9 a 33% fracture risk[19]. It is recommended by the British Orthopaedic Oncology Society (BOOS) that prophylactic fixation should be offered where appropriate[2], with a threshold of ≥9/12 generally accepted for lower limb lesions[19]. The reproducibility and validity of Mirels's score in the upper limb is questioned given the load bearing differences between upper and lower limbs. For instance, Howard et al proposed that the proportion of body weight a patient puts through the affected limb may predict fracture risk[13]. Furthermore, Kronisch et al suggest that using Mirels's to predict upper limb pathological fractures underestimates fracture risk[17]. Mirels's score does not take into account factors that influence load and functional demand, which has been shown to influence fracture potential[13]. In contrast, other studies have highlighted that up to 20% of impending pathological fractures may be missed or undergo unnecessary fixation but suggest Mirels's rating system is a valid, reproducible screening tool to identify impending pathological humerus fractures when used by physicians with differing levels of experience and specialty, as evidenced by Evans et al[11].

The aim of this study was to validate the accuracy and reproducibility of the Mirels's score in predicting metastatic fractures of long bones of the upper limb.

Materials and Methods

Study Design, Data Source and In/Exclusion Criteria

A retrospective cohort study (January 2013 to December 2018) was undertaken in all patients referred to an orthopedic department who had bone metastases of the upper limb long bones. Data was extracted from the Tayside Bony Metastasis Registry (TBMR) database. Patients were included if they had a radiologically visible lesion of any long bone of the upper limb and were confirmed or highly suspicious for metastatic cancer (including myeloma and hematological malignancies such as lymphoma). There were no upper or lower age limits. Patients were followed up until death or until December 2019, whichever was first.

Data extraction

Patient variables (patient age, gender, primary tumor diagnosis, location of metastasis, use of bisphosphonates, analgesic use and previous radiotherapy [any site]) were extracted from patient electronic case records including follow-up letters to determine outcome.

Raters

Raters comprised 6 clinicians of varying experience and specialty – two orthopedic registrars (KH and SD), two upper limb specialist trauma surgeons (JM and AJ), an orthopedic oncology surgeon (PC) and a consultant clinical oncologist (DA).

Mirels's analysis

For assessment of the radiological parameters of the Mirels's score, plain radiographs of the limb at presentation were downloaded from the Picture Archive and Communication System (PACS) server (Insignia, UK) and duplicated in two electronic folders. The radiographs were ordered randomly and scored on two occasions by six investigators (KH, SD, DA, PC, JM, AJ). Each investigator assessed the radiological parameters of the Mirels's score for each radiograph on two occasions two weeks apart after reading the original Mirels's publication[19]. Pain was retrieved from patient records and a score of 1 was given for site for

all lesions, as they all involved the upper limb. The range of possible Mirels's scores for lesions in this study was therefore 4-10. Our study utilization of the Mirels's criteria is different to the original paper but is what is commonly used in clinical practice.

Approvals

Caldicott Guardian approval was secured prospectively (ref IGTCAL3289).

Statistical Analysis

Missing data, where present, has been indicated. Where study groups have been directly compared with one another, dataset analysis comprised the Chi-square test for categorical variables and the student's t-test or non-parametric Wilcoxon test as appropriate for continuous variables (significance $p<0.05$). Data was analyzed using IBM® SPSS® Statistics (v25) (IBM, Armonk, NY, USA) and Fleiss' kappa test was used to calculate intra- and interobserver variability as per a previous study[5,13,14]. Assessment of strength of agreement amongst raters was determined using Cohen's kappa coefficient as follows: kappa value <0.20 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.00 very good[5]. Bland-Altman plots were generated using SPSS in order to demonstrate variance in radiological assessment of Mirels's parameters between the six raters, and linear regression analysis was used to indicate presence of bias[14].

Results

Upper limb bony metastases study population

From 2013-2018, 10,050 patients were referred to a Scottish regional trauma center (Figure 2). Of these patients, 2% (207/10,050) had a lesion suspicious for a bony metastasis. 45 patients had 46 bony metastases involving the upper limb long bones (45/207 22%). The mean age was 69 years (range 51-91 years) (Table 1). 17 (38%) were female and 28 (62%) were male. The commonest primary tumor diagnoses were lung (29% 13/45), prostate and hematological (both 20% 9/45). The location of upper limb metastases is shown in Table 1. The humerus was the most commonly affected site (76% 35/46 lesions), followed by the ulna (6.5% 3/46). One patient with breast cancer fractured twice (bilateral humeral fractures).

Overall patient mortality was 29% at 3 months and 73% at one year (13/45 and 33/45, respectively). Five patients were still alive with a mean follow-up of 2 years (range 10.7 months to 3 years). The median time from referral for bony metastasis to death for the 40 patients' deceased at follow-up was 4.3 months (interquartile range IQR 10.5-2, range 12 days to 3.1 years). For the 35 patients who fractured, the mean time from fracture to death was 6.8 months (SD 5.8, range 12 days to 1.5 years).

Overall rate of progression to surgery was 57% (26/46). Intramedullary nailing was the most common procedure undertaken for upper limb bony metastases (77% 20/26 Table 1).

Fracture Rate

The overall fracture rate was 76.1% (35/46). Where time from lesion diagnosis on radiograph to fracture was known (20/35), lesions occurred at a median 19 days from initial diagnosis (IQR 60-10, range 1 day to 2 years) (Table 2). Fracture rate rose from 45% at 6

weeks (14/31) to 52% at 3 months (16/31 odds ratio OR 1.3) and 55% at 6 months (17/31 OR 1.5).

A higher Mirels's score did not predict an increased likelihood of metastatic fracture (Mean Mirels's score for Fracture group 7.1 SD 1.4, range 4-10 and No fracture group 7.2 SD 1.7, range 5-10, respectively) (Table 2 and Figure 3). A Mirels's score of ≥9/12 did not accurately predict patients who would go on to fracture (11% 5/46 fracture rate for Mirels's 9 or more versus 65.2% 30/46 for Mirels's 8 or less, $p<0.001$). Almost two thirds of patients with a Mirels's score of 8 or less sustained a fracture (65% 30/46 Fracture group versus 17% 8/46 No fracture group, $p<0.001$). The sensitivity of the Mirels's score in upper limb lesions for scores ≥9 versus ≤8 was 14% and 73%, respectively (Table 3). Those patients with Mirels's score of ≥9/12 did not have preponderance to any specific primary tumor diagnosis.

When the Mirels's cut-off was lowered to ≥7, better prediction of fractures was demonstrated (48% 22/46 fracture rate for Mirels's ≥7 versus 11% 5/46 for Mirels's 6 or less, $p<0.001$) (Table 3). However, those with a score of 6 or less were still more likely to fracture than not (28% 13/46 Fracture group versus 13% 6/46 No fracture group, $p=0.037$). For scores ≥7 versus ≤6, sensitivity rose to 63% but specificity fell to 55%.

Intraobserver Variability

Table 4 demonstrates the kappa values for variability within raters between week 0 and week 2 (intraobserver variability). Kappa values for raters did not significantly differ between baseline (week 0) and week 2 ratings, so the week 0 values were used in the final analysis. There was fair agreement between the raters for lesion size and total Mirels's score, with poor agreement for radiological appearance (whether lesion was lytic, sclerotic or mixed on plain radiographs).

166

167 Bland-Altman plots were generated to allow visual comparison of individual rater scores
168 (Figure 4). These graphs demonstrated no intraobserver bias (linear regression coefficients
169 all close to 0), with no difference in variance by Mirels's score.

170 **Interobserver Variability**

171 Kappa values were calculated to determine interobserver variability for all radiological
172 parameters of the Mirels's score (lesion size, radiological appearance and total Mirels's
173 score) (Table 5). There was moderate agreement amongst raters for radiological appearance
174 and total Mirels's score, and good concordance for lesion size.

175

176 Bland-Altman plots demonstrate higher variance in individual component and total Mirels's
177 scores at the mid-range (6 and 7) (Figure 5). Linear regression coefficients are close to 0,
178 providing evidence that there is no inter-rater bias.

Discussion

Patient Cohort and Demographics

In concordance with the published literature, the humerus is the most common site for bone metastases of the upper extremity[1,21]. In our cohort, the percentage undergoing surgery was 57%. This is lower than expected given stabilization of pathological fractures is pain relieving, and considerably lower than the rate of proximal femoral lesions undergoing surgery in a comparable cohort (71% 138/195)[10]. In contrast, the overall fracture rate of 76% is considerably higher than that seen in lower limb lesions (57% 112/195)[10], which may reflect a higher rate of prophylactic fixation in lower limb lesions.

Mortality from referral for upper limb metastases is 29% at 3 months, suggesting there is window of opportunity to assess those patients that may benefit from prophylactic surgery. The type of surgery is comparable to the literature, with intramedullary nailing being the procedure of choice in most cases as it is reliable for both impending and fractured proximal humerii[3].

The overall fracture rate of 76% was high, which is in keeping with a lower rate of surgery (therefore a lower rate of prophylactic fixation) compared to lower limb lesions[6,10], although this has been incompletely quantified previously. In addition, the majority of lesions which went on to fracture did so within 3 months (16/20 80%), emphasizing the importance of the orthopedic referral as a ‘crisis point’ in the clinical progression of a known upper limb metastasis. This also highlights the importance of detection and prediction in a clinical setting to identify those patients early for operative management. It is well documented that patients undergoing elective, prophylactic surgery for an impending fracture have reduced

blood loss, cardiac events and in-hospital stay compared to those undergoing urgent, emergency surgery[1,14,23].

Mirels's Score for prediction of metastatic fractures in upper limb metastases

Many previous studies have focused on the validity of the Mirels's score in predicting metastatic fractures with mixed conclusions regarding the interobserver (reproducibility), intraobserver (repeatability) variability and predictive value of the score in identifying (A) those who will proceed to fracture and would benefit from surgery (positive predictive value) and (B) those who are unlikely to fracture and should not be subjected to unnecessary surgery (negative predictive value)[13].

Of studies focusing on the validity of the score in proximal femoral lesions, the most comprehensive is Howard et al, which demonstrated reasonable inter- and intraobserver variability of the Mirels's score in predicting per-trochanteric fractures[14]. However, they were also unique in assessing for bias and variability amongst raters, and concluded that even in the lower limb, Mirels's score has poor reproducibility and high subjectivity in predicting fractures.

MacNiocaill et al preceded this and included long bone metastases throughout the skeleton[18]. With a similar methodology to our current paper but utilizing only specialist orthopedic oncologists, they found moderate to good variability in radiological aspects of the Mirels's score in a sample size of 35 radiographs. However, they do not provide data on the number of upper limb lesions included in this series, they did not assess for rater bias and excluded the pain component of the Mirels's tool, scoring patients out of a maximum of 9[14,18].

The only previous study to assess validity of the Mirels's score specifically in upper limb metastases was published in 2008 by Evans and colleagues[11]. This study had a relatively

small sample size of 17 radiographic lesions assessed by a multidisciplinary group of clinicians and did not assess intraobserver variability. In addition, for interobserver variability, they showed fair agreement for lesion size, moderate for total Mirels's score and 'incomplete' results for radiographic lesion appearance. As a result, we cannot agree with their conclusion that the Mirels's score is reproducible and valid for humeral lesions. Of note, they did recommend a reduced Mirels's cut-off for surgery in upper limb lesions of ≥7/12, in contrast to the recommended cut-off of ≥9/12 for lower limb lesions[2,19]. This recommendation increased sensitivity of the score in upper limb lesions from 14.5 to 81% with a resultant reduction in specificity from 82.9 to 32%.

We report a similar trade-off with a reduction in the Mirels's cut-off from ≥9/12 to ≥7/12 (increased sensitivity from 15 to 63% with decreased specificity from 73% to 55%). We also report a 48% fracture rate with a ≥7/12 Mirels's cut-off, which is considerably higher than the 33% fracture rate necessitating consideration of prophylactic fixation recommended for lower limbs.

To our knowledge, this is the largest study on this specialist subject to date and the only one that fully evaluates the validity and reproducibility of Mirels's score in upper limb bony metastases. No previous studies focusing on the prognostic benefit of the Mirels's score in the upper limb have included as large a patient cohort as ours, nor have they correlated reliability of rater scores with resultant fracture rate. In addition, we collated scores from a multidisciplinary group of raters, not just orthopedic oncology specialists (as per the original intention of Mirels's in reporting the score)[14,19]. Our study is limited however in its reliance on retrospective reporting of pain from patient electronic records (introducing potential bias in the total Mirels's score). In addition, we acknowledge that this patient cohort includes only

253 those patients referred by oncology for a surgical opinion, therefore cannot be assumed to
254 represent all patients with upper limb bone metastases. We acknowledge that rates of
255 fracture may be associated with primary tumor histological diagnosis; this wasn't specifically
256 explored in the present paper.

Conclusions

We conclude that in patients referred to orthopedics for bone metastases of the upper limb, Mirels's score may not valid or reproducible. More importantly based on the results of our study we noted that it does not accurately predict risk of progression to pathological fracture. However, until a more valid scoring system has been developed, we recommend a Mirels's score threshold of ≥7/12 for consideration of prophylactic fixation of impending upper limb pathological fractures. A score of ≥7/12 for upper limb long bone metastases predicts a fracture rate of 48% with sensitivity of 63% and specificity of 55%. This is in contrast to the current threshold of ≥9/12 usually recommended for lower limb lesions.

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Figure and Tables

Figure 1

Mirels's score for predicting risk of pathological fracture in bone metastases of the appendicular skeleton. Initially described by Hilton Mirels's in 1989[19], this figure reproduced with permission from[9].

Figure 2

Flowchart summarizing participant identification and demographics.

Figure 3

Receiver operator characteristic (ROC) curve demonstrating diagnostic ability of Mirels's score for upper limb metastases. ROC curve lies along 45º diagonal line and area under the curve (AUC) is 0.51, demonstrating low accuracy of Mirels's score at all parameters (6-10) in predicting pathological fracture for upper limb lesions.

Figure 4

Bland-Altman plots showing intraobserver variability for all permutations of rater for a) total Mirels's score, b) radiographic appearance and c) lesion size. There is no difference in variance by Mirels's score. The dot-dash lines on the X axis at 2a, 2b and 2c demonstrate the linear regression coefficient (mean of differences) and as they are all close to 0, demonstrate the absence of bias in the results. The dashed lines represent the limits of agreement (LOA mean + 1.96 SD and mean - 1.96 SD) AKA 95% confidence intervals[15]. Jitter has been used to demonstrate individual observations.

Figure 5

Bland-Altman plots showing interobserver variability for a) total Mirels's score, b) radiographic appearance and c) lesion size. There is higher variance for Mirels's scores in the mid-range of values recorded (6 and 7). The dot-dash lines on the X axis at 2a, 2b and 2c demonstrate the linear regression coefficient (mean of differences) and as they are all close to

0, demonstrate the absence of bias in the results. The dashed lines represent the limits of agreement (LOA mean + 1.96 SD and mean - 1.96 SD) AKA 95% confidence intervals[15]. Jitter has been used to demonstrate individual observations.

Table 1

Table summarizing demographic data for all patients with upper limb bony metastases included in this study.

Table 2

Table showing the fracture rates in patients where time to fracture was known and fracture percentages for each calculated Mirels's score.

Table 3

Variation in sensitivity and specificity by Mirels's threshold for predicting risk of pathological fracture for upper limb bone metatases.

Table 4

Table highlighting intraobserver variability in lesion size, radiological appearance and Mirels's scores between scoring clinicians.

Table 5

Table highlighting overall interobserver variability in lesion size, radiological appearance and Mirels's scores.

Table 1

Demographic	Value
	n=45 patients unless otherwise specified
Mean age, yrs (range)	69 (51-91) n=45 patients
Male, n (%)	28 (62)
Female, n (%)	17 (38)
Site of Upper Limb Metastasis, n (%)	**n=46, total number of lesions**
Humerus	35 (76)
Ulna	4 (9)
Radius	2 (4)
Clavicle	1 (2)
Scapula	1 (2)
Multiple	3 (7)
Primary Cancer, n (%)	
Lung	13 (29)
Prostate	9 (20)
Haematological	9 (20)
Renal/urological	5 (11)
Breast	3 (7)
Bowel	2 (4)
Liver	2 (4)
Other	2 (4)
Surgery, n (%)	**n=46, total number of lesions**
Yes	26 (57)
No	20 (44)
Type of Surgery, n (%)	**n=26 patients who had surgery**
Intramedullary Nail	20 (77)
Plate	3 (12)
Other	3 (12)
Mortality from referral, n (%)	
6 weeks	8 (18)
3 months	13 (29)
6 months	22 (49)
1 year	33 (73)
Follow-up	
Range	11 months – 6.8 years
Mean (SD)	3.6 years (1.8)
Median (IQR)	3.2 years (5.4-2.2)

Table 2

	Value n=31, number of lesions where time to fracture/not fracture was known	Odds ratio	p value
Overall fracture rate	**n=46 lesions** 35 (76)	-	
Time Point			
6 weeks	14 (45)	-	
3 months	16 (52)	1.3	
6 months	17 (55)	1.5	
By Mirels' score	Fracture **n=35**	No fracture **n=10**	
Range	4-10	5-10	
Mean	7.1 (1.4)	7.2 (1.7)	
Median (IQR)	7 (8-6)	6 (8.5-6)	
4	1 (3)	0	0.161
5	0	1 (3)	0.161
6	6 (19)	5 (16)	0.376
7	3 (10)	0	**0.042**
8	7 (23)	2 (7)	**0.041**
9	2 (7)	2 (7)	0.5
10	1 (3)	1 (3)	0.5
Rate of metastatic fracture by Mirels' score			
	n=46 lesions		
	Fracture	No fracture	
5 or less	3 (7)	1 (2)	0.156
6 or more	32 (70)	10 (22)	**<0.001**
p value	**<0.001**	**0.002**	
6 or less	13 (28)	6 (13)	**0.037**
7 or more	22 (48)	5 (11)	**<0.001**
p value	**0.045**	0.376	
7 or less	18 (17)	6 (13)	**0.002**
8 or more	17 (37)	5 (11)	**0.002**
p value	0.416	0.376	
8 or less	30 (65)	8 (17)	**<0.001**
9 or more	5 (11)	3 (7)	0.232
p value	**<0.001**	0.056	

Table 3

Mirels' cut-off	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
≥6	91	9	76	25
≥7	63	55	82	32
≥8	49	55	77	25
≥9	14	73	63	21

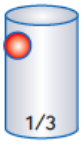
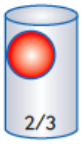
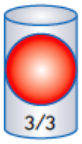
Table 4

	Observation 1		**Observation 2**		**Strength of agreement**
	Interobserver Variability (95% CI)	**p value**	Interobserver Variability (95% CI)	**p value**	
Lesion Size	0.358 (0.288-0.429)	<0.001	0.345 (0.276-0.415)	<0.001	Fair
Radiological appearance	0.107 (0.02-0.193)	0.015	0.114 (0.024-0.205)	0.014	Poor
Total Mirels' Score	0.274 (0.229-0.318)	<0.001	0.226 (0.180-0.272)	<0.001	Fair

Table 5

	Intraobserver Variability (95% CI)	Strength of agreement
Lesion Size	0.716 (0.432-0.999)	Good
Radiological appearance	0.427 (0.195-0.768)	Moderate
Total Mirels' Score	0.580 (0.395-0.765)	Moderate

Figure 1

Fracture		Score
Site	Upper limb	1
	Lower limb	2
	Proximal femur (peri-trochanteric)	3
Pain	Mild	1
	Moderate	2
	Functional (worse on use of limb)	3
	Sclerotic (blastic, gain of bone)	1
Lesion	Mixed (combination of sclerotic and lytic)	2
	Lytic (loss of bone)	3
Ratio of lesion to diameter of bone*	<1/3 diameter 1 	1/3-2/3 2 
		>2/3 diameter 3 
Total	8=15% fracture risk	**/12**
	9=33% fracture risk	

*Permeative or "moth-eaten" lesions can be poorly defined, multiple in nature, or ragged in appearance, and can be difficult to accurately quantify using this system.31 Seek specialist radiology or orthopaedic input for aid in classifying lesions if required

Figure 2

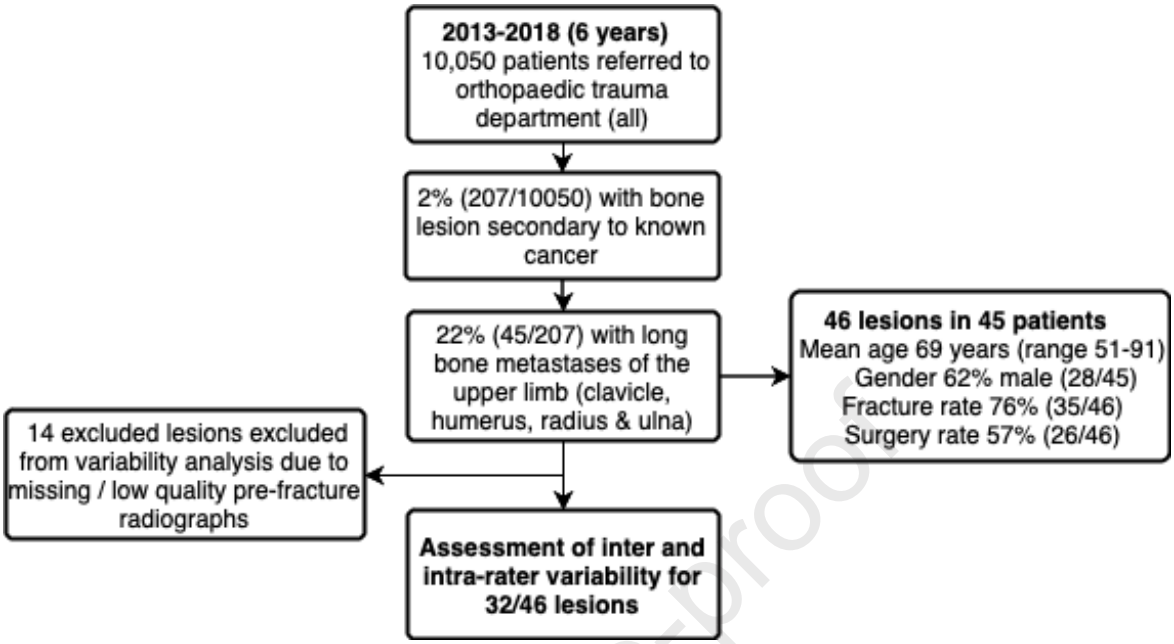


Figure 3

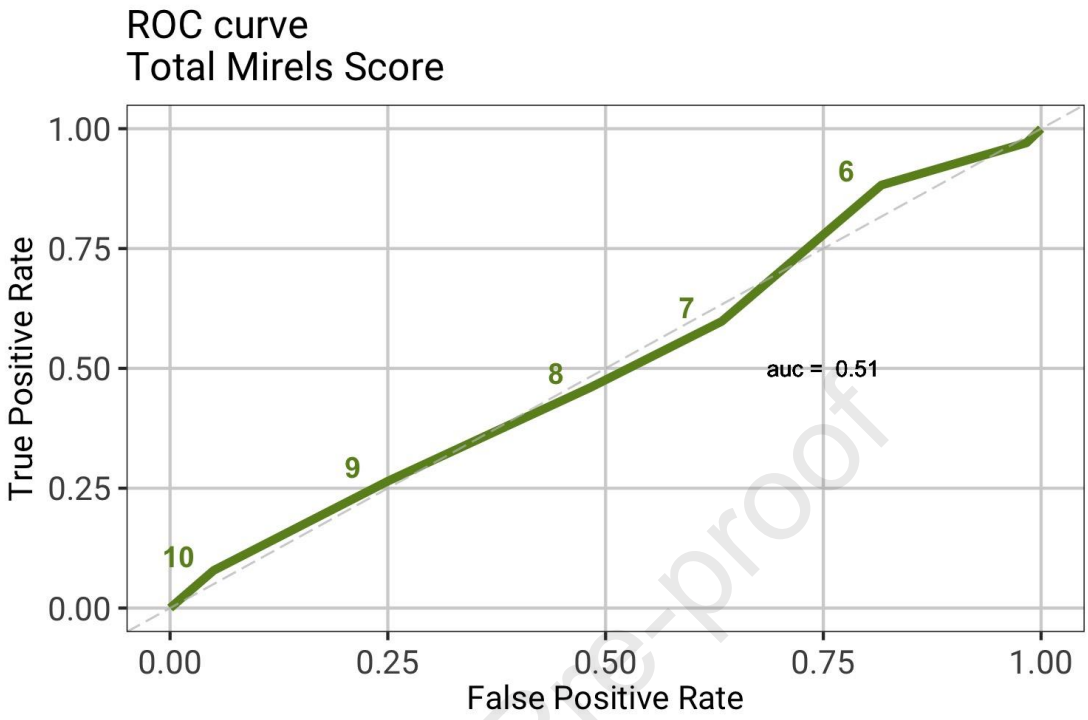


Figure 4

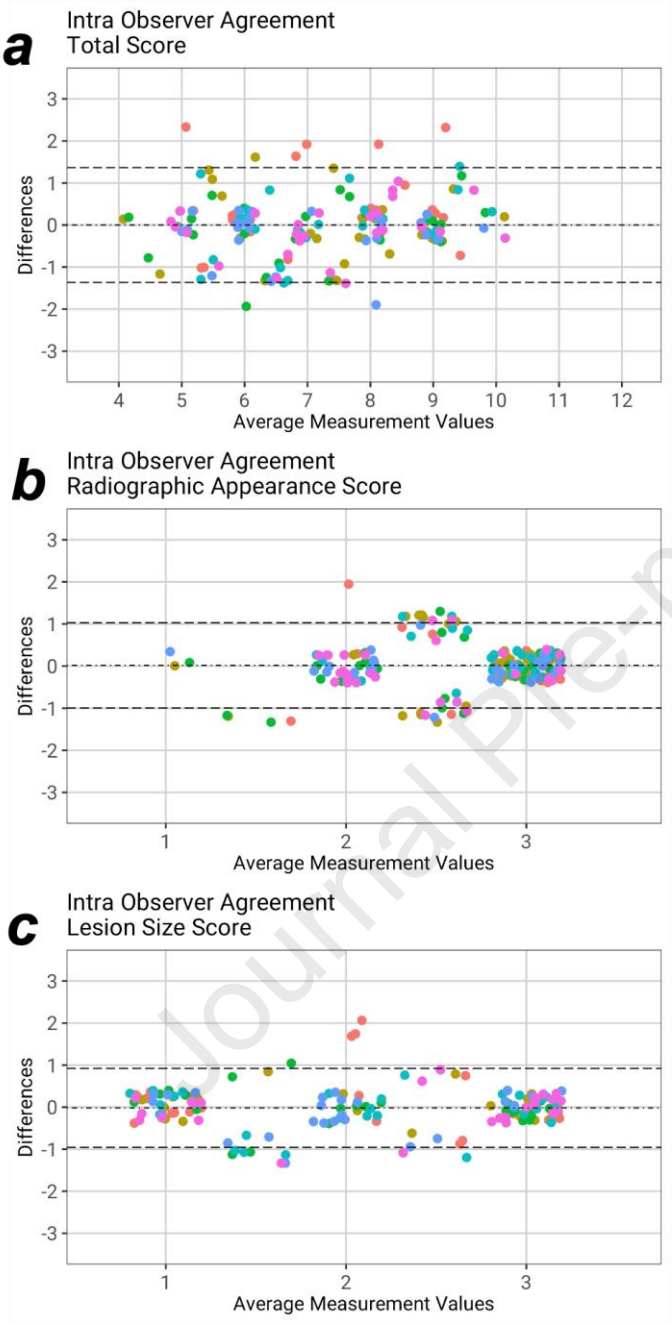


Figure 5