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Mirels' score for upper limb metastatic lesions: do we need a different cutoff for recommending prophylactic fixation?

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Hypothesis: The aim of this study was to investigate the reproducibility, reliability, and accuracy of Mirels' score in upper limb bony metastatic disease and validate its use in predicting pathologic fractures.
Methods: Forty-five patients with upper limb bony metastases met the inclusion criteria (62% male 28/45). The mean age was 69 years (SD 9.5), and the most common 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' score was calculated in 32 patients; with plain radiographs at index presentation scored using Mirels' system by 6 raters. The radiological aspects (lesion size and appearance) were scored twice by each rater (2 weeks apart). Intraobserver and interobserver reliability were calculated using Fleiss' kappa test. Bland-Altman plots compared the variances of both individual components and the total Mirels' 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 (interquartile range 60-10), and 80% (16/20) occurred within 3 months of diagnosis.
Mirels' score of ≥9 did not accurately predict lesions that fractured (fracture rate 11%, 5/46, for Mirels' ≥ 9 vs. 65%, 30/46, for Mirels' ≤ 8, $P < .001$). Sensitivity was 14%, and specificity was 73%. When Mirels' cutoff was lowered to ≥7, patients were more likely to fracture than not (48%, 22/46, vs. 28%, 13/46, $P = .045$); sensitivity rose to 63%, but specificity fell to 55%.
Kappa values for interobserver variability were $\kappa = 0.358$ (fair, 95% confidence interval [CI] 0.288-0.429) for lesion size, $\kappa = 0.107$ (poor, 95% CI 0.02-0.193) for radiological appearance, and $\kappa = 0.274$ (fair, 95% CI 0.229-0.318) for total Mirels' score. Values for intraobserver variability were $\kappa = 0.716$ (good, 95% CI 0.432-0.999) for lesion size, $\kappa = 0.427$ (moderate, 95% CI 0.195-0.768) for radiological appearance, and $\kappa = 0.580$ (moderate, 95% CI 0.395-0.765) for total Mirels' score.
Conclusions: This study demonstrates moderate to substantial agreement between and within raters using Mirels' score on upper limb radiographs. However, Mirels' 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' threshold of ≥7/12 for considering prophylactic fixation of

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impending upper limb pathologic fractures. This contrasts with the current ≥9/12 cutoff, which is recommended for lower limb pathologic fractures.

The most common cause of destructive bone lesions in the adult population is metastatic bone disease, with the humerus being the second most frequently involved long bone.[8,12] Pathologic 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' score, devised in 1989, provides a composite weighted scoring system (from 4 to 12) to predict the likelihood of sustaining a pathologic fracture based on pain, anatomical site, lesion size, and radiographic appearance (Fig. 1).[19] Mirels looked retrospectively at 38 patients with 78 long-bone metastases (classified by region as non-weight-bearing bone, weight-bearing bone, or pertrochanteric), with scores ≥8 recommending a 15% fracture risk and ≥9 a 33% fracture risk.[19] It is recommended by the British Orthopaedic Oncology Society 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' 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' score to predict upper limb pathologic fractures underestimates fracture risk.[17] Mirels' 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 pathologic fractures may be missed or undergo unnecessary fixation but suggest Mirels' rating system is a valid, reproducible screening tool to identify impending pathologic 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' score in predicting metastatic fractures of long bones of the upper limb.

Materials and methods

Study design, data source, and inclusion/exclusion criteria

A retrospective cohort study (January 2013-December 2018) was undertaken in all patients referred to an orthopedic department who had bone metastases of the upper limb long bones. Data were extracted from the Tayside Bony Metastasis Registry 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 of 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—2 orthopedic registrars (K.A.H. and S.D.), 2 upper limb specialist trauma surgeons (J.G.M. and A.C.J.), an orthopedic oncology surgeon (P.C.), and a consultant clinical oncologist (D.A.).

Mirels' analysis

For assessment of the radiological parameters of the Mirels' score, plain radiographs of the limb at presentation were downloaded from the Picture Archive and Communication System server (Insignia, UK) and duplicated in 2 electronic folders. The radiographs were ordered randomly and scored on 2 occasions by 6 investigators (K.A.H., S.D., D.A., P.C., J.G.M., A.C.J.). Each investigator assessed the radiological parameters of the Mirels' score for each radiograph on 2 occasions 2 weeks apart after reading the original Mirels' 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' scores for lesions in this study was therefore 4-10. Our study utilization of the Mirels' criteria is different to the original paper but is what commonly used in clinical practice.

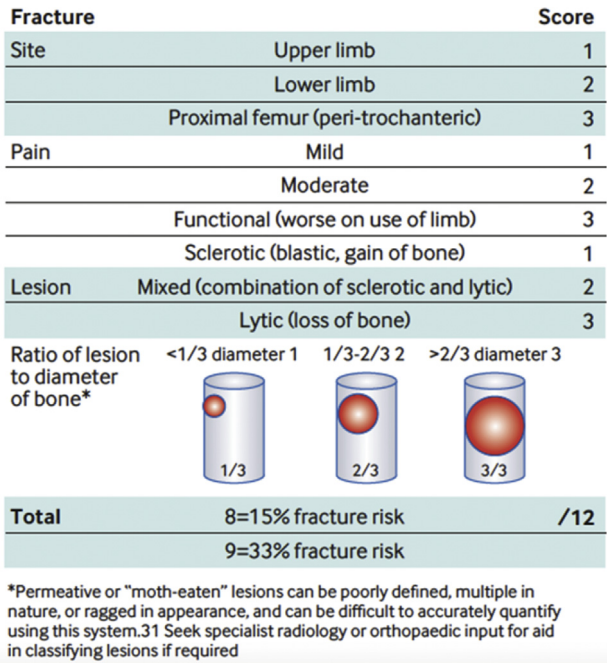

Figure 1 Mirels' score for predicting risk of pathologic fracture in bone metastases of the appendicular skeleton. Initially described by Hilton Mirels in 1989[19]; this figure is reproduced from [Diagnosis and referral of adults with suspected bony metastases, Downie S, Bryden E, Perks F and Simpson AHR, 372, page 7, 2021] with permission from BMJ Publishing Group Ltd.[9]

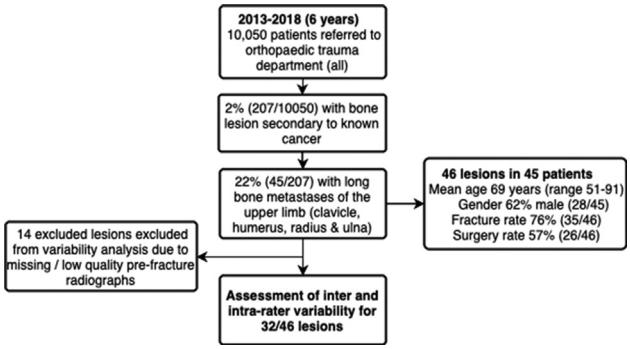

Figure 2 Flowchart summarizing participant identification and demographics.

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

Demographic	Value n = 45 patients unless otherwise specified
Mean age, yr (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)
Hematological	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 mo	13 (29)
6 mo	22 (49)
1 yr	33 (73)
Follow-up	
Range	11 mo – 6.8 yr
Mean (SD)	3.6 yr (1.8)
Median (IQR)	3.2 yr (5.4-2.2)

IQR, interquartile range; *SD*, standard deviation.

Approvals

Caldicott Guardian approval was secured prospectively (ref IGTCAL3289).

Statistical analysis

Missing data, where present, have been indicated. Where study groups have been directly compared with one another, data set analysis comprised the Chi-square test for categorical variables and the student's t-test or nonparametric Wilcoxon test as appropriate for continuous variables (significance $P < .05$). Data were analyzed using IBM SPSS Statistics (v25) (IBM, Armonk, NY, USA), and Fleiss' kappa test was used to calculate intraobserver and interobserver variability as per a previous study.[5,13,14] Assessment of strength of agreement among raters was determined using Cohen's kappa coefficient as follows: kappa value < 0.20 poor, 0.21-0.40 fair,

Table II
Fracture rates in patients where time to fracture was known and fracture percentages for each calculated Mirels' score.

Demographic	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 mo	16 (52)	1.3	
6 mo	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	.161
5	0	1 (3)	.161
6	6 (19)	5 (16)	.376
7	3 (10)	0	**.042**
8	7 (23)	2 (7)	**.041**
9	2 (7)	2 (7)	.5
10	1 (3)	1 (3)	.5
Rate of metastatic fracture by Mirels' score	n = 46 lesions Fracture	No fracture	
5 Or less	3 (7)	1 (2)	.156
6 Or more	32 (70)	10 (22)	**<.001**
P value	**<0.001**	**0.002**	
6 Or less	13 (28)	6 (13)	**.037**
7 Or more	22 (48)	5 (11)	**<.001**
P value	**0.045**	0.376	
7 Or less	18 (17)	6 (13)	**.002**
8 Or more	17 (37)	5 (11)	**.002**
P value	0.416	0.376	
8 Or less	30 (65)	8 (17)	**<.001**
9 Or more	5 (11)	3 (7)	.232
P value	**<0.001**	0.056	

IQR, interquartile range.
Bold indicates clinical significant value ($P < .05$).

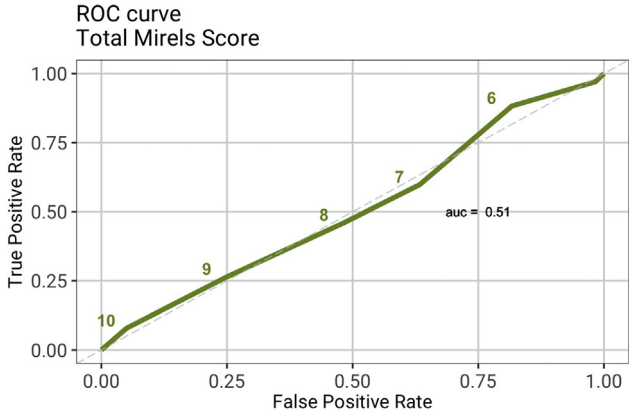

Figure 3 Receiver operator characteristic (*ROC*) curve demonstrating diagnostic ability of Mirels' score for upper limb metastases. ROC curve lies along 45° diagonal line, and area under the curve (*AUC*) is 0.51, demonstrating low accuracy of Mirels' score at all parameters (6-10) in predicting pathologic fracture for upper limb lesions.

Table III
Variation in sensitivity and specificity by Mirels' threshold for predicting risk of pathologic fracture for upper limb bone metastases.

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

Demographic	Observation 1	*P* value	Observation 2	*P* value	Strength of agreement
	Interobserver variability (95% CI)		Interobserver variability (95% CI)		
Lesion size	0.358 (0.288-0.429)	<.001	0.345 (0.276-0.415)	<.001	Fair
Radiological appearance	0.107 (0.02-0.193)	.015	0.114 (0.024-0.205)	.014	Poor
Total Mirels' score	0.274 (0.229-0.318)	<.001	0.226 (0.180-0.272)	<.001	Fair

CI, confidence interval.

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' parameters between the 6 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 (Fig. 2). Of these patients, 2% (207/10,050) had a lesion suspicious for a bony metastasis. Forty-five 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 I). Seventeen (38%) were female, and 28 (62%) were male. The most common 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 I. 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 1 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 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 I).

Fracture rate

The overall fracture rate was 76% (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 (interquartile range 60-10, range 1 day to 2 years) (Table II). 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' score did not predict an increased likelihood of metastatic fracture (mean Mirels' 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 II and Fig. 3). A Mirels' score of ≥9/12 did not accurately predict patients who would go on to fracture (11%, 5/46, fracture rate for Mirels' 9 or more vs. 65.2%, 30/46, for Mirels' 8 or less, $P < .001$). Almost two-thirds of patients with a Mirels' score of 8 or less sustained a fracture (65%, 30/46, fracture group vs. 17%, 8/46, no-fracture group, $P < .001$). The sensitivity of the Mirels' score in upper limb lesions for scores ≥9 vs. ≤8 was 14% and 73%, respectively (Table III). Those patients with a Mirels' score of ≥9/12 did not have preponderance to any specific primary tumor diagnosis.

When the Mirels' cutoff was lowered to ≥7, better prediction of fractures was demonstrated (48%, 22/46, fracture rate for Mirels' ≥ 7 vs. 11%, 5/46, for Mirels' 6 or less, $P < .001$) (Table III). However, those with a score of 6 or less were still more likely to fracture than not (28%, 13/46, fracture group vs. 13%, 6/46, no fracture group, $P = .037$). For scores ≥7 vs. ≤6, sensitivity rose to 63%, but specificity fell to 55%.

Intraobserver variability

Table IV 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' score, with poor agreement for radiological appearance (whether lesion was lytic, sclerotic, or mixed on plain radiographs).

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

Interobserver variability

Kappa values were calculated to determine interobserver variability for all radiological parameters of the Mirels' score (lesion size, radiological appearance, and total Mirels' score) (Table V). There was moderate agreement among raters for radiological appearance and total Mirels' score, and good concordance for lesion size.

Bland-Altman plots demonstrate higher variance in individual component and total Mirels' scores at the midrange (6 and 7)

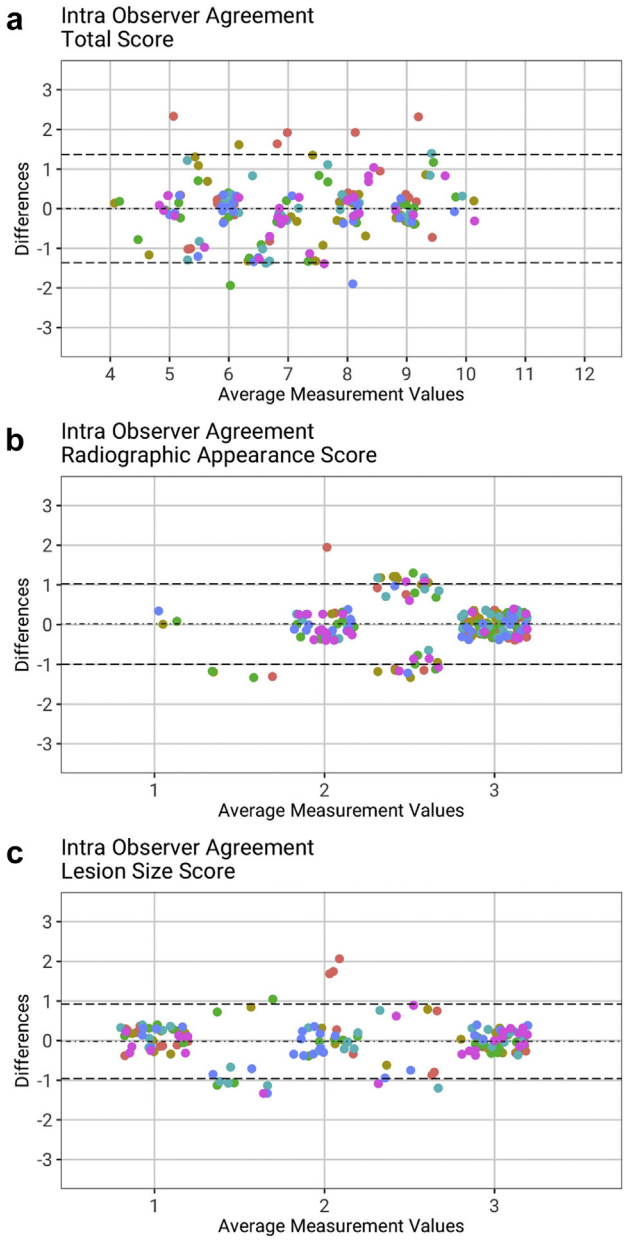

Figure 4 Bland-Altman plots showing intraobserver variability for all permutations of rater for (**a**) total Mirels' score, (**b**) radiographic appearance, and (**c**) lesion size. There is no difference in variance by Mirels' score. The dot-dash lines on the x-axis at 2a, 2b, and 2c demonstrate the linear regression coefficient (mean of differences), and as they are all close to 0, they 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) or 95% confidence intervals.[15] Jitter has been used to demonstrate individual observations.

(Fig. 5). Linear regression coefficients are close to 0, 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 pathologic fractures is pain relieving and considerably lower than the rate of proximal

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

	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

CI, confidence interval.

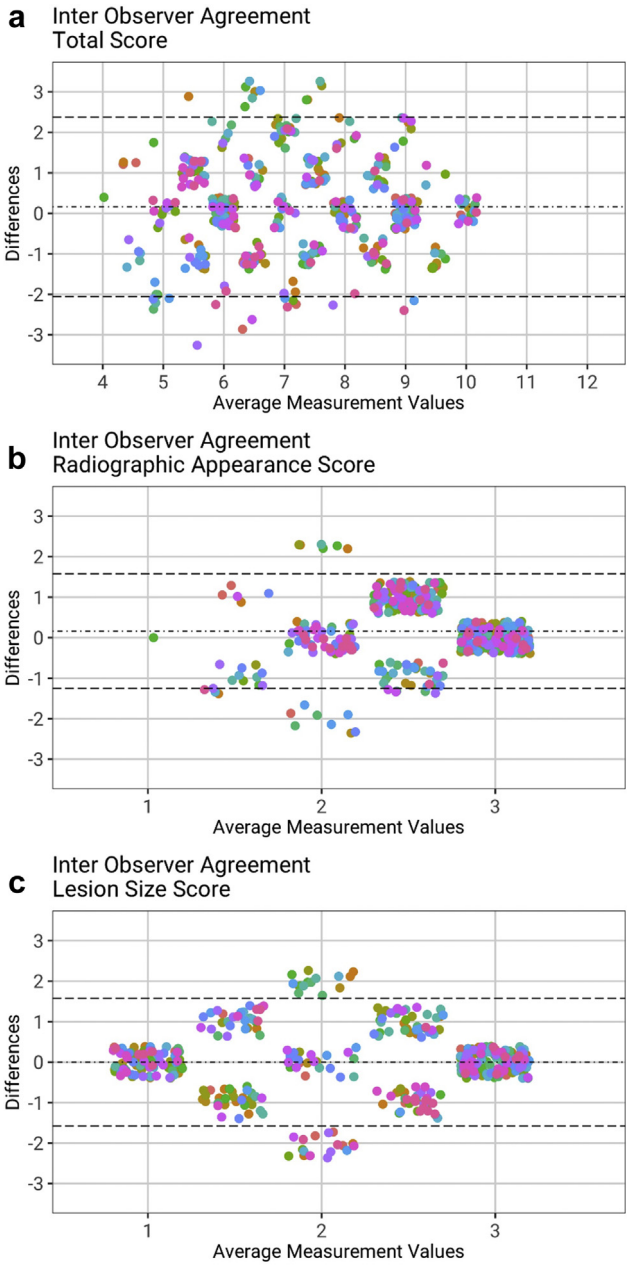

Figure 5 Bland-Altman plots showing interobserver variability for (**a**) total Mirels' score, (**b**) radiographic appearance, and (**c**) lesion size. There is higher variance for Mirels' scores in the midrange of values recorded (6 and 7). The dot-dash lines on the x-axis at 2a, 2b, and 2c demonstrate the linear regression coefficient (mean of differences), and as they are all close to 0, they 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) or 95% confidence intervals.[15] Jitter has been used to demonstrate individual observations.

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 a 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 surgeries for an impending fracture have reduced blood loss, cardiac events, and in-hospital stay compared to those undergoing urgent, emergency surgeries.[1,14,23]

Mirels' score for prediction of metastatic fractures in upper limb metastases

Many previous studies have focused on the validity of the Mirels' score in predicting metastatic fractures with mixed conclusions regarding the interobserver (reproducibility) and 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 the studies focusing on the validity of the score in proximal femoral lesions, the most comprehensive is the one by Howard et al, which demonstrated reasonable interobserver and intraobserver variability of the Mirels' score in predicting pertrochanteric fractures.[14] However, they were also unique in assessing for bias and variability among raters and concluded that even in the lower limb, Mirels' score has poor reproducibility and high subjectivity in predicting fractures.

Mac Niocaill 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' 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' tool, scoring patients out of a maximum of 9.[14,18]

The only previous study to assess validity of the Mirels' score specifically in upper limb metastases was published in 2008 by Evans et al.[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' score, and "incomplete" results for radiographic lesion appearance. As a result, we cannot agree with their conclusion that the Mirels' score is reproducible and valid for humeral lesions. Of note, they did recommend a reduced Mirels' cutoff for surgery in upper limb lesions of $\geq$7/12, in contrast to the recommended cutoff of $\geq$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' cutoff from $\geq$9/12 to $\geq$7/12 (increased sensitivity from 15%-63% with decreased specificity from 73%-55%). We also report a 48% fracture rate with a $\geq$7/12 Mirels' cutoff, 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' score in upper limb bony metastases. No previous studies focusing on the prognostic benefit of the Mirels' score in the upper limb have included as large a patient cohort as ours, nor have they correlated reliability of rater scores with the 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 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' score). In addition, we acknowledge that this patient cohort includes only those patients referred by oncology for a surgical opinion, therefore cannot be assumed to represent all patients with upper limb bone metastases. We acknowledge that rates of fracture may be associated with primary tumor histological diagnosis; this was not specifically explored in the present paper.

Conclusions

We conclude that in patients referred to orthopedics for bone metastases of the upper limb, Mirels' score may not be valid or reproducible. More importantly, based on the results of our study, we noted that it does not accurately predict risk of progression to pathologic fractures. However, until a more valid scoring system has been developed, we recommend a Mirels' score threshold of $\geq$7/12 for consideration of prophylactic fixation of impending upper limb pathologic fractures. A score of $\geq$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 $\geq$9/12 usually recommended for lower limb lesions.

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