Correlation Analysis of The Risk Factors for Pathological Fracture Using Mirels' Classification in Long Bone Metastatic Disease

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Abstract

Background: Pathological fracture is one of the consequences from MBD, which can worsen the prognosis and can deplete the quality of patients' lives. Looking at those effects, predicting the pathological fracture in MBD patients needs to be done. Objective: Determine the correlation of risk factors for pathological fractures in long bone metastatic disease and determine the accuracy of the Mirels' scoring system. Method: This was a retrospective research based on the medical record data and x-ray photos of patients with long bone metastases at Dr. Soetomo General Academic Hospital in 2019-2021. We determined the correlation of risk factors by using the likelihood-ratio test. Result: Of the total of 39 long bone metastases cases, there were 28 cases (71.79%) followed by pathological fracture, and 11 of them (28.21%) were not. From the calculation of Mirels' score, 36 cases had scores of ≥ 9 (impending), and 3 of them had scores of 8 (borderline). Most metastases were located in the lower extremities (48.7%), sized >2/3 cortex (48.7%), lytic type (79.5%), and with functional pain (82.1%). *%).* Conclusion: There was a correlation between the location of upper extremity lesions sized > 2/3 cortex, lytic type, and functional pain with the incidence of fracture ($p < 0,05$) and the percentage of Mirel's scoring system accuracy in predicting the incidence of pathological fractures was 66.67%.

Keywords: Long bone metastases; pathological fracture; Mirels' scoring; MBD

1. Introduction

Metastatic bone disease is a type of cancer from primary tumor cells from an area that spread to the bone[(1)]. Bone is the third most common site of metastases after the lungs and liver. Breast and prostate cancer are responsible for most bone metastases incidence. Bone metastases are one of the leading causes of morbidity[(2)]. It usually causes severe pain, impaired mobility, and a high chance of bone complications, such as pathologic fracture incidence[(3)]. Pathologic fractures are not caused by excessive pressure but by weakened bone due to a tumor[(4)]. The incidence of bone metastases followed by pathologic fractures can cause the patient to have a worsened quality of life, increased anxiety, and increased depression[(5)].

The potential effects make predicting the risk of pathologic fractures in patients with bone metastases important[(6)]. One of the methods that can be used to predict the risk is Mirel's scoring system or Mirel's classification system. The system can predict the risk of pathologic fracture based on four variables that are

believed to contribute to the risk of pathologic fracture: site, size, type, and pain level. These variables will then be assessed with progressive scores ranging from 1 to 3. The scores then accumulated with a maximum value of 12[7].

This study aims to analyze the correlation between risk factors on long bone metastases and pathologic fracture incidence using Mirel's classification and to determine the accuracy of Mirel's scoring system. The analysis results can be a reference for the community and health professionals to prevent fractures and reduce morbidity.

2. Methods

This paper was analytic retrospective research of metastatic bone disease patients at the Radiology department and Orthopaedic and Traumatology Department, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The data was based on the medical record and x-ray photos of patients with long bone metastases at Dr. Soetomo General Academic Hospital from January 2019 until October 2021. Patients diagnosed with long bone metastases, with or without pathological fracture, were included as the research's subjects. This study was approved by the Research Ethics Committee of Dr. Soetomo General Academic Hospital with number 0656/LOE/101.4.2/2021.

Using SPSS software, the Chi-Square test, all samples that met the inclusion criteria were analyzed to determine the correlation of risk factors for pathological fractures in long bone metastatic disease and to determine the accuracy of Mirel's scoring system.

3. Results

Based on the data, 39 patients with long bone metastases, both with and without pathological fractures, fit the inclusion criteria.

Table 1. Distribution of gender and age of patients with long bone metastases

Characteristics	N	%
Gender		
Male	12	30,77%
Female	27	69,23%
Age		
Mean	51,16	-
Youngest	5	-
Oldest	68	-
<25	1	2,56%
25-50	15	38,46%
>50	23	58,97%

The data showed that there are more female patients than male patients. There were 27 female patients (69.23%) and 12 male patients (30.77%). Based on the age group, the highest proportion was found in > 50 years old patients, with 23 cases (58.97%). The oldest patient was 68 years old, with long bone metastases from cervical tumors, and the youngest was 5 years old, with long bone metastases from nephroblastoma tumors.

Table 2. Distribution of primary tumors in patients with long bone metastases

Primary tumor	N	%

Breast	9	23,08%
Lung	8	20,51%
Thyroid	8	20,51%
Soft tissue	4	10,26%
Renal	2	5,13%
Pancreas	2	5,13%
Adrenal	1	2,56%
Esophagus	1	2,56%
Rectum	1	2,56%
Cervix	1	2,56%
Multiple myeloma	1	2,56%
Unknown origin	1	2,56%

The most common cause of long bone metastases in patients at Dr. Soetomo General Academic Hospital from 2019-2021 was breast tumors, followed by lung and thyroid tumors.

Table 3. Distribution of metastatic sites in long bones

Location	**N**	**%**
Femur	17	43,59%
Humerus	11	28,21%
Tibia	8	20,51%
Fibula	3	7,69%

The most site of metastasis was on the femur (43.59%), followed by the humerus bone (28.21%), tibia bone (20.51%), and fibula bone (7.69%).

Table 4. Distribution of histopathological examination results

Histopathology Examination	**N**	**%**
Adenocarcinoma	11	28,21%
Lung	5	12,82%
Breast	1	2,56%
Rectum	1	2,56%
Esophagus	1	2,56%
Multiple myeloma	1	2,56%
Renal clear cell	1	2,56%
Unknown origin	1	2,56%
Ductal	8	20,51%
Follicular thyroid	6	15,38%
Neuroendocrine	5	12,82%
Squamous cell carcinoma	5	12,82%
Lung	4	10,26%
Breast	1	2,56%
Papillary thyroid	2	5,13%
Cortical adrenal	1	2,56%
Nephroblastoma	1	2,56%

Based on the histopathological results, the highest percentage was adenocarcinoma (28.21%), with lung adenocarcinoma having the highest proportion, followed by ductal (20.51%), and follicular thyroid (15.38%).

Table 5. Characteristics of metastatic lesions in long bone metastatic patients

Lesion Characteristics	N	%
Location according to Mirels' scoring system		
Upper limb	11	28,21%
Lower limb	19	48,72%
Trochanteric region	9	23,08%
Size		
<1/3 of cortex	9	23,08%
1/3-2/3 of cortex	11	28,21%
>2/3 of cortex	19	48,72%
Type		
Blastic	0	0,00%
Mixed	8	20,51%
Lytic	31	79,49%
Pathological fracture		
With	28	71,79%
Without	11	28,21%

The highest prevalence of lesions characteristic were lesions located in the lower limb with 19 cases (48.72%), followed by lesions sized more than 2/3 of the cortex with 19 cases (48.72%), lytic lesions with 31 cases (79.49%), and lesions that followed by pathological fractures with 28 cases (71.79%).

Table 6. Pain level in patients with long bone metastases

Pain Scale	N	%
VAS score		
0,5-4,4	0	0,00%
4,5-7,4	7	17,95%
7,5-10	32	82,05%
Mean	8,7	-
Pain scale according to Mirels' scoring system		
Mild	0	0,00%
Moderate	7	17,95%
Functional	32	82,05%

Based on the data, the majority (82.05%) of patients had VAS scores of 7.5-10 and were in the functional pain category. The average VAS score in patients with long bone metastases at Dr. Soetomo General Academic Hospital in 2019-2021 was 8.71.

Table 7. The total score of patients with long bone metastases based on the Mirels scoring system

Total score	N	%
≤ 7 (*not impending*)	0	0,00%
8 (*borderline*)	3	7,69%
≥ 9 (*impending*)	36	92,31%

A total of 36 samples had a score of ≥ 9 and were in the impending fracture category (92.31%), and 3 samples had a score of 8 and were in the borderline category.

The Chi-Square statistical test using SPSS software found a correlation between the location of upper extremity with the incidence of pathological fractures (p = 0.003). The statistical tests also found a correlation between lesions in the upper extremities sized more than 2/3 of the cortex with the incidence of pathological fractures (p = 0.014). For the type of lesion, there was a correlation between the lytic type of upper extremity lesions with the incidence of pathological fractures (p = 0.003). For the pain level, there was a correlation between lesions in the upper extremities with functional pain levels and the incidence of pathological fractures (p = 0.005), and also there was a correlation between lesions in the lower extremities with functional pain levels and the incidence of pathological fractures (p = 0.044).

Table 8. Calculation of the accuracy of Mirels scoring system

		Score Prediction Result			Total	% of prediction accuracy
		Not impending	Borderline	Impending		
Observation result	With no pathological fracture	0	1	10	11	
	With pathological fracture	0	2	26	28	
	Total	0	3	36	39	**66,67%**

Of 39 patients, 11 did not experience pathological fractures, and 28 had pathological fractures. Of the 11 patients who did not have pathological fractures, according to Mirels' classification, 1 was in the borderline category, and 10 were in the impending fracture category. Of the 28 patients with pathological fractures, according to the Mirels classification, 2 were in the borderline category, and 26 were in the impending fracture category. The percentage of total accuracy calculated was 66.67%.

4. Discussion

In this study, the data showed that there are more female patients than male patients. There were 27 female patients (69.23%) and 12 male patients (30.77%). According to the research by Yang et al. (2016), of 3223 patients with bone metastases, 1708 were female (53%), and 1515 were male (47%)[8]. A systematic review by Farach-Carson et al. (2017) stated that sex hormone such as estrogen influence the pathogenesis of primary tumor growth and bone metastases[9]. The data in this study found that the highest number of primary tumors causing long bone metastases were breast tumors, which were only found in female patients. Based on the age group following the study by Yang et al., the highest proportion of age groups was patients aged 50-70 years old[8].

The distribution of the primary tumors revealed that the most common tumors that cause long bone metastases were breast and lung tumors. Similar to research from the University of South Florida by Henderson Jackson et al. (2016), the highest prevalence of primary tumors that cause long bone metastases was breast tumors, with 20 patients (24%), followed by lung tumors (19%)[10]. Unlike the research by Yang et al. (2016), the highest prevalence of primary tumors was lung tumors (36.5%), followed by breast tumors (30.9%) and prostate tumors (8.5%)[8]. Based on the research by W. Z. Chen et al. (2017), the site of long bone metastases from breast tumors was mainly in the femur, with 81 cases (24.8%)[11]. Bone metastases from breast tumors were mainly osteolytic type and pathological fractures were common in patients with metastases from breast tumors[12,13]. A study by Zhou et al. (2017) found that the most common site for long bone metastases from lung tumors was the femur, with 71 of 108 cases metastasizing to the long bones[14]. Most long bone metastases from lung tumors showed osteolytic lesions on radiological images[15]. It indicated that pathological fractures were skeletal-related events that often occur in patients with primary lung

tumors[16]. The data in this study found that the most common metastases occurred in the femur. The result was similar with the study by Shimada et al. (2014), in which 50 cases of long bone metastases, 56% of cases occurred in the femur, 32% in the humerus, and 12% in the tibia[17]. Based on the histopathological examination in this study, most of the tumors were the adenocarcinoma type. Based on the research by Hui et al., the histopathological examination with the highest prevalence was adenocarcinoma types (52%), followed by thyroid carcinoma types which were divided into follicular and papillary carcinomas[18]. In this study, the second highest prevalence was the ductal type. It happened because breast tumors caused most long bone metastases cases. The American Cancer Society (2021) stated that histologically, more than 75% of breast tumor cases were of the ductal type[19].

Bone metastases are the most common cause of pain in patients with malignant diseases[20]. Thus, Mirels included the pain level in the scoring system[7]. The average VAS score in patients with long bone metastases at Dr. Soetomo General Academic Hospital in 2019-2021 was 8.71 (functional pain). This study's results are similar to the study by Hiba et al. (2022), which stated that the average VAS score of 117 patients was 8.7 ± 1.5[20]. Clinical analysis showed that osteolytic lesions were closely related to the occurrence of pain. Osteoclast activity is under the influence of tumor necrosis factor-alpha (TNF alpha) and other cytokines secreted by cancer cells. Then the osteoclasts secrete protons and acidic enzymes that break down the bone. The acidic environment activates nociceptors which give rise to the perception of pain[21].

After calculating using the Mirels' scoring system, 36 samples (92.31%) scored ≥ 9 and were classified in the impending fracture category. It indicated that most patients with long bone metastases at Dr. Soetomo General Academic Hospital in 2019-2021 were likely to experience a pathological fracture. It happened because Dr. Soetomo General Academic Hospital is a type A hospital with the highest referral in Eastern Indonesia[22]. It may be why most of the patients with long bone metastases were in a complex or severe condition, marked by the accumulated Mirels score of more than 9.

Statistically, there was a correlation between the site of lesions in the upper extremities with the incidence of pathological fractures ($p = 0.003$) and there was a correlation between lesions in the upper extremities sized more than 2/3 of the cortex with the incidence of pathological fractures ($p = 0.014$). It happened because more than half of the samples (72.7%) in the upper extremities had lesions that are more than 2/3 of the cortex, while only 42.1% of the samples in the lower extremities and only 33.3% of the samples in the trochanteric area were larger than 2/3 of the cortex. Hoban et al. (2022) stated that the lesion size had a significant relationship with the incidence of pathological fractures ($p < 0.001$)[23]. For the type of lesion variable, it was found that there was a correlation between the lytic type lesions in upper extremities with the incidence of pathological fractures ($p = 0.003$). In this study, all cases (100%) of metastases in the long bones of the upper extremities were having the lytic type. According to Mirel's original literature, cases of long bone metastases with lytic lesions were significantly associated with the incidence of pathological fractures[24]. Lytic lesions can occur due to tumors' osteoclast activation, which results in increased RANKL ligand activity. Lytic lesions often cause pathological fractures due to biomechanical changes and cause the bones to be weak and fractures[25]. For the pain level variable, there was a correlation between lesions in the upper extremities with functional pain levels and the incidence of pathological fractures ($p = 0.005$), and there was a correlation between lesions in the lower extremities with functional pain levels and the incidence of pathological fractures ($p = 0.044$). In the study by Evans et al. (2008), the risk factor for pain level correlated significantly with the incidence of pathological fracture ($p < 0.0001$)[26]. There was a close relationship between the level of functional pain and the lesion size, where 90% (19 out of 21) of patients who experienced functional pain had lesions sized more than 2/3 of the cortex[24]. In this study, most lesions in the upper and lower extremities were sized more than 2/3 of the cortex, whereas, in the trochanteric area, only one-third of cases with a size of more than 2/3 of the cortex.

This study found that the percentage of total accuracy of the scoring system from Mirels was 66.67%. Based on Howard, Cool, and Cribb (2019), the specificity of the scoring system from Mirels is around 35%[27]. Other studies said that the specificity of the Mirels scoring is 50%, and the sensitivity is 71%[28]. In

this study, things that could be the cause were because Dr. Soetomo General Academic Hospital is a type A hospital and is the highest referral hospital in Eastern Indonesia. So patients who came to Dr. Soetomo Hospital tend to be in a severe and compex condition[22]. In addition, the level of health-seeking behavior in Indonesia is still relatively low, and Indonesians prefer non-formal health providers (e.g., traditional medicine, acupuncture, massage, and hypnotherapy)[29]. It probably why in this study, many patients with long bone metastases came with pathological fractures.

This research has several limitations. First, the sample distribution was not equal in each variable and relatively limited. Second, there were samples with large lesion sizes that involved the lower extremities and trochanteric areas, making it difficult to deduce the site of the lesion. Based on Howard, Cool, and Cribb (2019), the boundary between the lower extremities and the trochanteric was not written in the original literature, so it is quite difficult to decide whether the lesion was in the lower extremities or trochanteric[27]. Thus, a similar study with a larger number of samples with a more equal sample distribution is needed.

Currently, the latest techniques for predicting pathological fractures are CT-based structural rigidity analysis (CTRA) and finite element analysis (FEA). The CTRA and FEA techniques have a much higher specificity and sensitivity than the Mirels scoring. Respectively, the specificity and sensitivity of CTRA are 60-90% and 100%. Respectively, the specificity and sensitivity of FEA are 63-86% and 80-100%. However, these two techniques have yet to be widely used because they need sophisticated technology and technical expertise, take more time, and are expensive[30].

Until this day, Mirels' scoring system is still widely used to help predict the incidence of pathological fractures since the calculation method is simple. Regardless, it needs to be combined with other assessments and not solely just the Mirels scoring to avoid unnecessary prophylactic surgery[31].

5. Conclusion

There was a correlation between the location of upper extremity lesions sized > 2/3 cortex, lytic type, and functional pain with the incidence of fracture. There was also a correlation between lesions in the lower extremities with functional pain with the incidence of pathological fractures ($p < 0.05$). The accuracy percentage of pathological fracture prediction on the Mirels scoring system was 66.67%. The Mirels scoring system is relatively easy and a good predictor in assisting the practice of pathological fracture management in long bone metastases. However, it needs to be combined with other assessments and not solely just the Mirels scoring to avoid unnecessary prophylactic surgery.

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