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New scoring system as predictor of 90-day mortality in appendicular skeletal metastases

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ABSTRACT

Introduction. Cancer is one of the most common causes of death worldwide and occurs through the ability of malignant neoplasm cells to leave the primary tumor site and spread to other parts of the body through a complex process known as metastases. However, the decision to do surgery is dilemmatic due to the surgical risk, mortality rate, and cost control, especially in a developing country.

Material and methods. A case control was investigated in our tertiary referral hospital from patients in 2013–2021. Of the 113 eligible patients, 24% (27) patients died within 3 months of their fracture. Medical records were reviewed in detail specifically for patient's age, Karnofsky score, Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), types of the primary tumor, and metastases to another organ. Chi-square followed by multivariate analysis using backward elimination method were performed. Further ROC analysis was done to assess the sensitivity and specificity of the novel scoring system.

Results. High CRP, LDH, and additional metastases to another organ besides the bone are the significant predictors of 90-day mortality after a pathological fracture due to bony metastases. A total score of 5 or lower has 78% specificity to predict a 90-day mortality after a pathological fracture due to bony metastases.

Conclusions. Focus to palliative should not be commenced when a total score of 5 or lower is found. Future prospective multicenter studies would help establish the validity of this novel scoring system.

Key words: metastatic bone disease, pathological fracture, mortality

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Introduction

Cancer is one of the most common causes of death worldwide and occurs through the ability of malignant neoplasm cells to leave the primary tumor site and spread to other parts of the body through a complex process known as metastasis. The resulting pathological fractures increasingly require attention in the field of musculoskeletal oncology because of their increasing incidence, which is mainly due to the availability of better diagnosis and treatment of metastatic diseases, resulting in a longer survival rate [1, 2]

Ninety-day mortality is often used as a measure of quality of care, especially in terminal illnesses with limited therapeutic options related to resources and socioeconomics, such as liver transplantation for end-stage liver cirrhosis [3]. The decision to do orthopedic surgery in such cases is dilemmatic due to the surgical risk, mortality rate, and cost control, especially in a developing country. Moreover, clinicians' ability to predict prognosis in patients with metastatic bone disease is poor, with a reported accuracy of only 18% [4].

There have been several scores that have been developed in the field of orthopedic oncology, but none

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have been designed to predict mortality within 3 months after the occurrence of pathological fractures.

Our specific goals were to examine predictors of 90-day mortality in patients with appendicular skeletal metastases, and how factors should be put together as a useful scoring system so that it has a practical utility in clinical settings.

Material and methods

Study design and setting

We performed a case-control study using data from our tertiary referral hospital from 2013 to 2021. The study was approved by our university's ethical review board. After searching our database, all patients with the initial diagnosis or their relatives were contacted via telephone to ask for research consent, authorization for using their medical records, and the current condition of the patients.

Participants/study subjects

The exclusion criteria were patients with pathological fractures that were not caused by a metastatic tumor, patients on corticosteroid therapy, bisphosphonate therapy prior to the fracture, and those who had received operative fixation of the associated long bones before the occurrence of the pathological fracture. Incomplete data were counted as drop-outs. Taken together, 16% of patients (21) were excluded from the study. With all patient consent received, the final study samples comprised 113 patients with pathological fractures due to skeletal metastases treated between January 1, 2013 and December 31, 2021.

Data collection

Demographic and clinical data were obtained from our electronic hospital database, including some laboratory and radiographic details that were done outside of our hospital. Karnofsky Performance Scale (KPS) was routinely assessed in cancer patients and well-documented in the paper-based medical records of our hospital. Diagnoses of pathological fracture were made using plain X-ray, while metastases were diagnosed using the combination of abdominal ultrasonography and magnetic resonance imaging. Primary tumor types were determined either with core biopsy results or analysis of the histopathological tissue obtained during subsequent surgeries. They were then classified further according to Bollen et al. [5]. Serum lactate dehydrogenase (LDH) and C-reactive protein (CRP) were also routinely assessed in our hospital and were considered high if exceeding 250 IU/L and 4 mg/dL, respectively.

The patient's age was defined in accordance with the patient's identity card recorded in the hospital database, with 60 years of age used as the cut-off of old age [6, 7]. The recorded KPS [8] of 20 or less was considered as a potential risk factor, as well as the presence of any metastases, primary tumor with a rapid-growth type, high serum LDH and CRP. Mortality was defined as death within 90 days after the diagnosis of pathological fracture.

Chi-square analysis for each potential risk factor was then performed, followed by multivariate analysis using logistic regression and the backward elimination method. The statistically significant risk factors were then divided by each of their Exp(b) values to simplify the numerical value without reducing its proportional significance. Further, receiver operating characteristic (ROC) analysis was performed to assess the sensitivity and specificity of the novel scoring system. All statistical analysis of the data was done using SPSS version 24 (IBM Corp, Armonk, NY, USA) with $\alpha = 0.05$ regarded as the statistical threshold for significance.

Results

Univariate analysis showed that the association between 90-day mortality and pathological fracture due to bony metastases was higher for patients who have a high value of CRP (OR: 11.27, 95% CI, 1.45–87.49; p = 0.05) and LDH (OR: 8.4, 95% CI, 1.07–65.71; p = 0.018) compared to patients with normal values. Furthermore, patients with any presence of metastasis in another organ in addition to the pathological fracture had a higher risk of mortality (OR: 3.76, 95% CI, 1.43–9.23; p = 0.005) compared to patients who had only skeletal metastases. No differences were observed in the risk of 90-day mortality between patients with older age (OR: 1.73, 95% CI, 0.72–4.16; p = 0.216), low KPS (OR: 0.587, 95% CI, 0.20–1.73; p = 0.33), and more aggressive (rapid-type) primary tumor (OR: 2.19, 95% CI, 0.89–5.37; p = 0.083) compared to patients who were younger, with higher KPS, or had moderate, less aggressive (slow-type) primary tumor (Tab. 1).

Further multivariate analyses, with the same adjustments, were performed to determine significant risk factors from each univariate analysis, resulting in the exponential of logistic regressions [Exp(B)]. Serum LDH had the highest association [Exp(B) = 8.99, 95% CI, 1.09–73.62; p = 0.041] with 90-day mortality after pathological fracture due to bony metastases, followed by serum CRP [Exp(B) = 8.57, 95% CI, 1.06–68.98; p = 0.044], and the presence of other metastases [Exp(B) = 3.36, 95% CI, 1.25–9.03; p = 0.016] (Tab. 2).

Table 1. Result of univariate analysis using the Chi-Square Method

	Status		p	OR (95% CI)
	Alive/Mortality after 90 days	Mortality within 90 days		
Age				
> 60 y.o.	30 (34.9%)	13 (48.1%)	0.22	1.73 (0.72–4.16)
≤ 60 y.o.	56 (65.1%)	14 (51.9%)		
KPS				
< 30	24 (27.9%)	5 (18.5%)	0.33	0.587 (0.2–1.73)
≥ 30	62 (72.1%)	22 (81.5%)		
LDH (IU/L)				
> 250	65 (75.6%)	26 (96.3%)	0.021	8.400 (1.07–65.71)
≤ 250	21 (24.4%)	1 (3.7%)		
CRP (mg/dL)				
> 4	60 (69.8%)	26 (96.3%)	0.05	11.267 (1.45–87.49)
≤ 4	26 (30.2%)	1 (3.7%)		
Another metastasis				
Positive	34 (39.5%)	19 (70.4%)	0.005	3.632 (1.43–9.23)
Bone-only	52 (60.5%)	8 (29.6%)		
Primary tumor type				
Rapid	23 (26.7%)	12 (44.4%)	0.08	2.191 (0.89–5.37)
Mild-Moderate	63 (73.3%)	15 (55.6%)		

OR — odds ratio; CI — confidence interval; LDH — lactate dehydrogenase; CRP — C-reactive protein; KPS — Karnofsky Performance Scale

Table 2. Result of multivariate analysis using the backward stepwise method in logistic regression

	Exp(B)	95% CI for Exp(B)	
		Lower	Upper
LDH	8.99	1.09	73.62
CRP	8.57	1.06	68.98
Metastasis	3.36	1.25	9.03

LDH — lactate dehydrogenase; CRP — C-reactive protein; CI — confidence interval

To simplify the numerical value without reducing its proportional significance, the value of each Exp(B) was divided by the least significant value of Exp(B) (3.36) and rounded to the nearest integer. Therefore, each patient could be scored between 0 and 7, depending on the summation of their abnormal serum CRP (3 points), abnormal serum LDH (3 points), or presence of other metastases (1 point) (Tab. 3). Receiver operating characteristic (ROC) analysis was performed to assess the sensitivity and specificity of this novel scoring system, showing the area under the ROC Curve (AUC) greater than 0.7 (Fig. 1). With the use of the numerical threshold of 6, the specificity and sensitivity of this scoring system were 77.9% and 66.7%, respectively. Therefore, a patient who has a total score of 5 or lower would be 7.05 times more likely to die within 90 days after a pathological fracture due to bony metastases (Tab. 4).

Table 3. The novel scoring system

Clinical findings	Score
LDH	
≤ 250 IU/L	0
> 250 IU/L	3
CRP	
≤ 4 mg/dL	0
> 4 mg/dL	3
Additional metastases other than bone	
Absent	0
Positive	1
Total score	

LDH — lactate dehydrogenase; CRP — C-reactive protein

Discussion

Pathological fractures due to metastatic bone disease are an increasing problem in musculoskeletal oncology due to their increasing incidence [9, 10]. The dilemma is whether to do surgery given the surgical risk, mortality rate, and cost burden of orthopedic implants. These conisderations are especially relevant in developing countries, such as ours, where the GDP is only 6% of the US' and there is an increasing rate of poverty: 1.63 million people compared to September 2019 and an 1.28 million people compared to March 2019 [6].

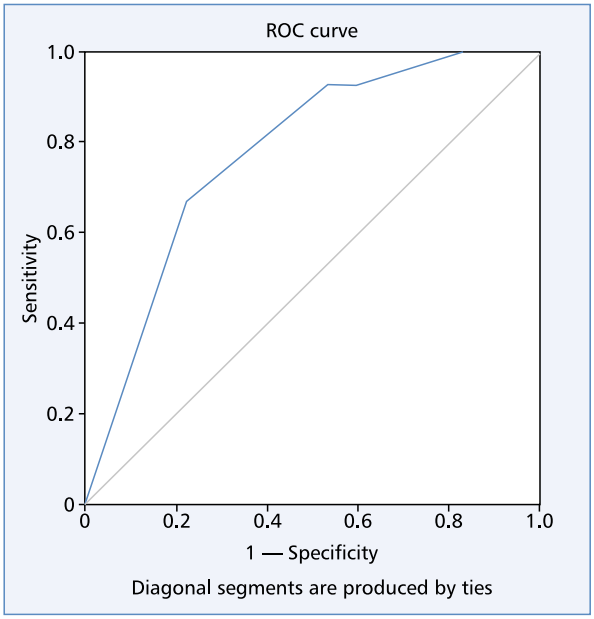

Figure 1. Receiver operating characteristic (ROC) curve

Table 4. Specificity and sensitivity test

		Status		Total
		Alive/Mortality after 90 days	Mortality within 90 days	
Total score	≥ 6	18	19	37
		66.7%	22.1%	32.7%
	< 6	9	67	76
		33.3%	**77.9%**	67.3%
Total		27	86	113
		100.0%	100.0%	100.0%

Ninety-day mortality is often used as a measure of the quality of care, especially in terminal illnesses with limited therapeutic options related to resources and socioeconomics, such as liver transplantation for end-stage liver cirrhosis [3]. Therefore, a scoring system based on affordable, routine and readily-available examinations would be a tremendous help in decision-making in such dilemmatic situations. Our newly developed score is based on the significance of the high value of serum CRP, LDH, and the presence of metastases to another organ besides the bone as the predictors of 90-day mortality after a pathological fracture due to metastases in appendicular bones.

This study has limitations, most notably the data originated from a single tertiary center with retrospective reporting on a relatively small number of patients. A nationwide data would supposedly generate a larger and more diverse sample of the population, but maintaining strict quality control in the extraction of such data is still a tremendous challenge in our country at present. Nevertheless, the number of samples in the study was still sufficient to represent the targeted population according to the WHO [7, 11].

Predictors of 90-day mortality after a pathological fracture due to bony metastases

LDH is found in almost every cell in the body, converting lactate to pyruvate in the glycolysis process. When a cell dies, it becomes extracellular and can be detected in the blood. Thus, dead cell increase reflects a proportional number of tissue injuries and could be caused by various diseases — one of which is cancer [12]. A worse prognosis related to the high serum LDH level was found statistically significant in our study, specifically as marker of 90-day mortality. Similarly, a higher risk of mortality related to the high level of serum LDH has been reported in pancreatic cancer [13], prostate cancer [14], breast cancer [15–17], and many other tumors [18, 19].

Another significant outcome in this study that can be used to predict poor prognosis is CRP levels. Few studies included laboratory data as prognostic factors especially CRP levels in patients with cancer. Nemecek et al. [20] in 2018 had done research on how CRP can predict the survival rate. They conclude that CRP is statistically significant in predicting the survival rate in patients with bone tumors: patients with pre-operative CRP levels $\geq$ 1.0 mg/dL had a lower survival rate than patients with CRP levels < 1 mg/dL ($p = 0.026$) [20]. In the recent study by Errani et al., pathological CRP was also found to be a negative independent prognostic factor in patients with long bone metastases, along with types of the primary tumor [21]. As reported by Avnet et al [22], the exact processes and mechanismes behind the CRP in which cancer itself seems to directly induce permanent inflammation, are still unknown. However, inflammation could also lead to tumor progression and metastasis [22].

The presence of metastases in other extraskeletal organs was also a significant predictor to assess the risk of mortality in patients with MBD in this study. Other authors showed that visceral metastases correlate with the survival rate [23, 24]. Compared with metastases to another organ, metastases to the bone had, indeed, more favorable survival prognoses.

Old age, rapid-type primary tumor, and KPS were found to be insignificant predictors of 90-day mortality in this study [25–30]. These results were different from other studies, which might be caused by our shorter time frame of mortality and different pathologic fractures, specifically targeting appendicular bones, instead of spinal metastases. Therefore, they were not included as items in our prognostic scoring.

Scoring system

The goal of our study was to make a practical scoring system that can be helpful in decision-making in pathological fractures of the appendicular skeleton due to metastatic bone disease. Most of the existing scoring systems were designed to aid decision-making in spinal metastases or did not specifically address the appendicular skeleton [31–34]. While others [21, 35, 36] had different time frame for mortality that did not correspond well with the situation of a developing country, such as ours. With numerous advanced cases due to late diagnosis or neglect, a high number of complications, and a high burden of implant cost, palliative care must always be considered the best resolution for the patient with a total score of 6 or higher, who is 7-fold more likely to die within 90 days. This new scoring system would facilitate solving such dilemmas with scientific rationale, instead of clinical prediction which has poor reliability.

Conclusions

This new scoring system is a useful predictor of 90-day mortality in patients with appendicular skeletal metastases, especially in developing countries. Future prospective multicenter studies would help to cement the validity of this novel scoring system for broader use.

Conflict of interest

All authors declare no conflicts of interest.

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