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Research Article

Prognostic factors and real-life applicability of prognostic models for patients with bone metastases of carcinoma

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ABSTRACT

Objective: This study aimed to investigate the factors affecting the survival of patients with bone carcinoma metastases and assess the clinical applicability of existing prognostic models.

Methods: We retrospectively evaluated 247 patients who presented to our hospital between 2011 and 2021 diagnosed with bone carcinoma metastasis. Demographic data, general health status, primary diagnoses, laboratory and radiological findings, pathological fracture status, treatment methods, and survival times of the patients were recorded, and the effects of these variables on survival time were evaluated. Previously developed Katagiri, Janssen, 2013-Spring, PathFX, and SORG prognostic models were applied, and the predictive performances of these models were evaluated by comparing the predicted survival time with the actual survival time of our patients.

Results: After the multivariate analysis, the following factors were shown to be significantly associated with the survival time of patients: blood hemoglobin and leukocyte levels, lactate dehydrogenase concentration, prognostic nutritional index, body mass index, performance status, medium and fast-growing groups of primary tumors, presence of extraspinal and visceral or brain metastases, and pathological fractures. According to receiver operating characteristics and Brier scores, SORG had the overall highest performance scores, while the Janssen nomogram had the lowest.

Conclusion: Our report showed that all prognostic models were clinically applicable, but their performances varied. Among them, the SORG predictive model had the best performance scores overall and is the model the authors suggested for survival prediction among patients with carcinoma bone metastases.

Level of Evidence: Level IV, Prognostic Study.

Introduction

Survival of cancer patients has increased significantly along with newly developed effective treatment options. Thus, it has also increased the incidence of cancer-related complications and metastases. Bone is the third most common site of metastasis after lung and liver, and median survival after diagnosis of bone metastasis ranges from approximately 1 year for patients with lung cancer to 3-5 years defined for breast and prostate cancers.[1]

Metastatic bone lesions can cause pain or spinal compression due to microfractures or the pressure effect of the space-occupying mass itself. While metastases may cause significant decreases in the quality of life with such mechanisms, they may also be life-threatening because of metabolic effects such as hypercalcemia or cytopenia due to bone marrow involvement. Metastasis-related conditions and the associated need for intervention are defined as skeletal-related events.[2]

The main goal of treatment for bone metastases is symptom palliation and to prevent disease progression; cure is rarely aimed for. Palliative treatments are preferred in end-stage patients with short survival expectation.[1,3,4] Surgical treatment indications include pathological fracture, impending fracture, spinal cord compression, or persistent pain. The primary diagnosis, number of metastases, and expected survival time determine the surgery that will be performed.[5-7]

Many studies have been conducted to predict the survival that will guide treatment in patients with metastatic bone diseases. As a result, many scoring systems such as Katagiri scores,[8,9] SORG[10] and PathFX[11] web applications, 2013-Spring,[12] and Janssen[13] nomograms were proposed. However, none of these predictive systems were shown to be superior to another.

In this study, we aimed to assess the possible prognostic factors and their effects on survival in cancer patients with bone metastases, the predictive performance of prognostic models, and their real-life applicability, which could guide the surgeon to determine the appropriate treatment.

Materials and Methods

This study was conducted with the approval of the local Non-interventional Clinical Research Ethics Committee of Çukurova University as the 13th

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decision of the meeting numbered 106, dated 04 December 2020. Informed consent was obtained from all patients at the time of surgery or biopsy. Our study has a level of evidence of 3, and the report was designed according to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guideline.

Patients who were admitted to Çukurova University Hospital between 2011 and 2021 with histologically confirmed carcinoma bone metastases were included in our study. The medical data of patients was investigated. The exclusion criteria were determined as lack of laboratory data or whole-body scan [positron emission tomography–computed tomography (PET-CT) or bone scintigraphy], treatment at another center, and being lost to follow-up before 12 months due to reasons other than death (Figure 1).

Patients' pathological diagnosis, ages, surgical history, genders, body mass index (BMI) categories (underweight, normal, obese), American Society of Anesthesiology (ASA), and Eastern Cooperative Oncology Group (ECOG) scores, other systemic diseases, treatments applied before or after detection of metastases [chemotherapy, hormonal therapy, external radiotherapy (ERT)], dates of the last follow-up and death were recorded. For some models, it was required to convert ECOG scores to Karnofsky scores.[14] Survival times were calculated as the time elapsed between the dates of diagnosis of bone metastases or surgery; and the dates of death or last follow-up for survivors.

HIGHLIGHTS

- Many scoring systems such as were proposed to guide treatment in patients with metastatic bone disease. This study aimed to assess the possible prognostic factors and their effects on survival in cancer patients with bone metastases and performances of prognostic models.
- The results showed significant associations between patient survival and factors like blood metrics, nutritional and performance status, tumor characteristics, and metastases. Moreover, the SORG model had the best performance scores while the Janssen nomogram had the lowest.
- The results indicate that while all models in the study are applicable in clinical settings for survival time estimation, the SORG machine learning system demonstrated superior predictive accuracy and is recommended for use in survival prediction.

Blood samples were obtained at the time of bone metastasis detection. The prognostic nutritional index (PNI) was also calculated.[15]

Metastatic sites were detected by whole-body scans obtained at the time of diagnosis, and visceral and/or brain (VBM) and lymph node (LNM) metastases were detected with PET-CT, additional computed tomography (CT), or magnetic resonance imaging performed at the same admission.

Age was categorized as under 65 and 65 or higher. The ASA and ECOG scores were dichotomized (1-2 and 3-4, 0-1 and 2-4, respectively). The presence of systemic diseases other than carcinoma was also categorized into 2 groups as present or absent.[13]

The primary cancers were divided into 3 groups: rapid, moderate, and slow growth, as defined by Katagiri.[9] The existing reports of scans were used as criteria to avoid bias.

Scapula, clavicle, sternum, ribs, vertebrae, and pelvic bones were classified as axial; proximal metaphyses of the femur and humerus as proximal long bones (PLB); and regions distal to PLB as distal long bones (DLB). These metastatic sites were grouped into 6 categories: axial-only, PLB-only, DLB-only, axial with PLB, axial with DLB, and axial with PLB and DLB. In addition, 2 groups were also formed according to the presence of DLB metastasis to evaluate whether the distal metastases had an additional contribution to survival. The status of spinal involvement was classified into 2 groups: presence or absence of extraspinal bone metastasis. The presence of extraskeletal metastasis was also categorized as absent, LNM, or VBM. History of systemic therapy and bone-directed ERT was evaluated as received or not received. Associations of these variables with overall survival were statistically evaluated.

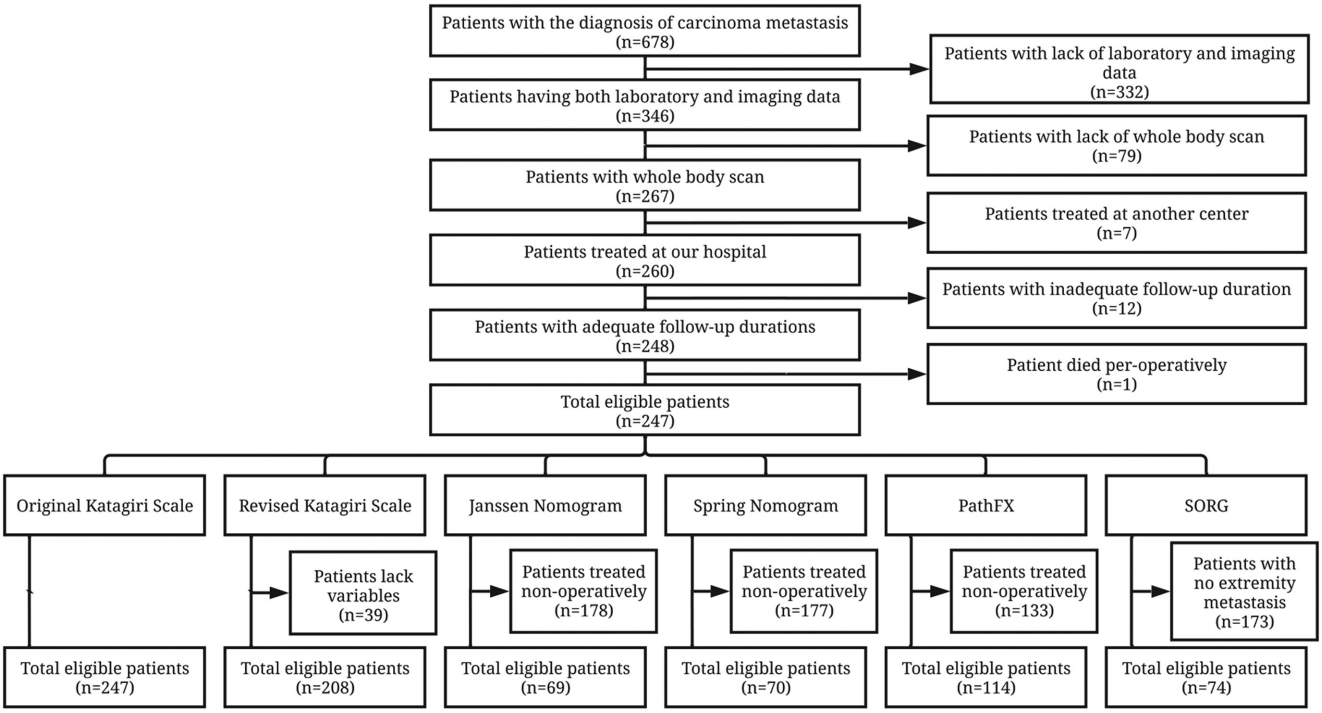

Figure 1. Flowchart of exclusion criteria.

The original[8] and revised[9] Katagiri scores, SORG[10] and PathFX[11] web applications, 2013-Spring,[12] and Janssen[13] nomograms were studied as predictive models. Patients who were ineligible for the prognostic model (no surgical treatment, no extremity metastases, missing data, etc.) were excluded from the evaluation of the related model (Figure 1). The estimated survival rates were compared with the patients' actual survival, and the survival prediction performances of these scales were evaluated statistically.

Receiver operating characteristic (ROC) analysis was performed to determine the appropriate cutoff point for the PNI value, and the PNI variable was divided into 2 groups according to this value.[16]

Kaplan-Meier analysis and Cox regression analysis were performed to examine the relationship between overall survival time. Potential risk factors and the relevant hazard ratios (HR) were also obtained.

Prognostic models, their parameters and outcome features with time intervals were summarized in Table 1. ROC analysis and area under the curve (AUC) values were obtained. Also, Brier scores were calculated to assess the performances of predictive models. AUC values were interpreted as indiscriminate for 0.5 and lower, bad for 0.5-0.6, sufficient for 0.6-0.7, good for 0.7-0.8, very good for 0.8-0.9, and excellent for values higher than 0.9.[17] Brier score is between 0 and 1; and lower scores are associated with better performances while a score more than 0.25 indicates the prediction as indiscriminate.[18]

Statistical Package for the Social Sciences Statistics version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) package program was used for statistical analyses. The statistical significance level was determined as .05 in all tests.

No funding was received from any agency or person for our research.

Results

A total of 247 patients were included in our study. Demographic features, data about the general health conditions of patients, and the distribution of laboratory values and the missing data are given in

Table 1. Parameters and outcome features of prognostic models

Model	Original Katagiri model	Revised Katagiri model	PathFX
Parameters	ECOG performance score Multiple skeletal metastases Previous chemotherapy Primary diagnosis Visceral / brain metastases	ECOG performance score Laboratory data[1] Multiple skeletal metastases Primary diagnosis Previous chemotherapy Visceral / brain metastases	Age ECOG performance score Gender Laboratory data[2] Lymph node metastases Number of skeletal metastases Pathological fracture Physician's estimate of survival Primary diagnosis Visceral metastases
Outcomes	6 months o.a. survival rate 12 months o.a. survival rate 24 months o.a. survival rate	6 months o.a. survival rate 12 months o.a. survival rate 24 months o.a. survival rate	1 month p.o. survival rate 3 months p.o. survival rate 6 months p.o. survival rate 12 months p.o. survival rate 18 months p.o. survival rate 24 months p.o. survival rate
Model	**SORG**	**Janssen nomogram**	**2013-Spring nomogram**
Parameters	Age Brain metastasis Laboratory data [3] Previous systemic therapy Primary tumor histology Visceral metastasis	Age Body mass index category Hemoglobin level Other bone metastases Other comorbidity Primary tumor type Visceral / brain metastasis	ASA score group Hemoglobin level Karnofsky performance score Multiple metastases Pathological fracture Primary cancer growth Visceral metastases
Outcomes	6 months o.a. survival rate 12 months o.a. survival rate	1 month p.o. survival rate 3 months p.o. survival rate 12 months p.o. survival rate	3 months p.o. survival rate 6 months p.o. survival rate 12 months p.o. survival rate

ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group, o.a., overall, p.o., post-operative.
[1]**Laboratory data:** Albumin, C-Reactive protein, calcium, lactate dehydrogenase, platelet, total bilirubin.
[2]**Laboratory data:** Absolute lymphocyte count, hemoglobin.
[3]**Laboratory data:** Absolute lymphocyte count, absolute neutrophile count, albumin, alkaline phosphatase, calcium, creatinine, hemoglobin, platelet, sodium, white blood cell count.

Table 2. Categorization of demographic data and laboratory results

Age (years), n (%)		**ECOG score, n (%)**	
<65	168 (68)	0-1	193 (78.1)
≥65	79 (32)	2-4	54 (21.9)
Gender, n (%)		**ASA score, n (%)**	
Female	107 (43.3)	1-2	190 (76.9)
Male	140 (56.7)	3-4	57 (23.1)
Additional disease, n (%)		**Body mass index, n (%)**	
Present	100 (40.5)	Underweight	62 (25.1)
Absent	147 (59.5)	Normal	139 (56.3)
CEA, n (%)		Obese	46 (18.6)
Normal	66 (26.7)	**Corrected calcium, n (%)**	
High	120 (48.6)	Normal	168 (68)
Loss	61 (24.7)	High	52 (21.1)
CA19-9, n (%)		Loss	27 (10.9)
Normal	92 (37.2)	**Calcium, n (%)**	
High	37 (15)	Normal	229 (92.7)
Loss	118 (47.8)	High	15 (6.1)
CA125, n (%)		Loss	3 (1.2)
Normal	72 (29.1)	**Phosphorus, n (%)**	
High	64 (25.9)	Normal	173 (70)
Loss	111 (44.9)	Low	22 (8.9)
CA15-3, n (%)		Loss	52 (21.1)
Normal	65 (26.3)	**Creatinine, n (%)**	
High	58 (23.5)	Normal	210 (85)
Loss	124 (50.2)	High	37 (15)
Hemoglobin, n (%)		**Albumin, n (%)**	
Normal	89 (36)	Normal	114 (46.2)
Low	158 (64)	Low	107 (43.3)
WBC, n (%)		Loss	26 (10.5)
Normal	73 (29.6)	**Total bilirubin, n (%)**	
High	174 (70.4)	Normal	211 (85.4)
ALC, n (%)		High	17(6.9)
Normal	201 (81.4)	Loss	19 (7.7)
Low	46 (18.6)	**ALP, n (%)**	
Platelets, n (%)		Normal	134 (54.3)
Normal	229 (92.7)	High	88 (35.6)
Low	18 (7.3)	Loss	25 (10.1)
Sodium, n (%)		**LDH, n (%)**	
Normal	133 (53.8)	Normal	139 (56,3)
Low	110 (44.5)	High	79 (32)
Loss	4 (1.6)	Loss	29 (11.7)
PNI, n (%)		**CRP, n (%)**	
Normal	77 (34.8)	Normal	43 (17.4)
Low	144 (58.3	High	125 (50.6)
Loss	26 (10.5)	Loss	79 (32)

N=247.
ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ASA, American Society of Anesthesiologists; CA, cancer antigen; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PNI, prognostic nutritional index; WBC, white blood cell.

Table 2. The cutoff value of PNI was defined as 47.5. For this value, the sensitivity was defined as 71% and the specificity as 73%.

At the time of admission, 108 (43.7%) patients had no primary tumor diagnosis. Seventy-four (30%) of the cases had slow, 49 (19.8%) had moderate and 124 (50.2%) had rapid-growth pattern. The primary diagnoses and their distribution among genders are shown in Table 3.

While 115 patients had undergone surgery, 132 patients were treated non-surgically. Ninety-eight (39.7%) patients received systemic therapy before diagnosis, 155 (62.8%) after diagnosis, for a total of 174 patients (70.4%) who received systemic therapy.

A total of 215 (87%) patients died during follow-up, and the median age of death was 61 (25-87). The median follow-up period of the survivors was 44.1 months (12.1-121.9). The median overall survival time was 10.5 months (6 days-100.6 months), and postoperative survival was 4.8 months (3 days-68.8 months) for patients who had undergone surgery. In addition, the survival rate of our patients was 94.7% at 1 month; 77.3% at 3 months; 64.4% at 6 months; 31.3% at 12 months and 12.2% at 24 months (Figure 2).

The numbers of eligible patients for prognostic models are shown in the flowchart (Figure 1). Postoperative or overall actual survival durations were considered according to the features of the related predictive system.

Table 3. Distribution of primary tumor diagnoses by groups and gender

Diagnostic group	Diagnosis	Gender		
		Female n (%)	Male n (%)	Total n (%)
Slow growing	Breast (hormone dependent)	56 (22.7)	-	56 (22.7)
	Prostate (hormone dependent)	-	13 (5.3)	13 (5.3)
	Thyroid cancer	4 (1.6)	1 (0.4)	5 (2)
	Total	60 (24.3)	14 (5.7)	74 (30)
Moderate growing	Renal cell carcinoma	8 (3.2)	6 (2,4)	14 (5.7)
	Lung cancer (receiving molecular targeted therapy)	4 (1.6)	8 (3.2)	12 (4.9)
	Prostate (hormone independent)	-	11 (4,5)	11 (4,5)
	Breast (hormone independent)	9 (3.6)	-	9 (3.6)
	Endometrial cancer	2 (0.8)	-	2 (0.8)
	Ovarian cancer	1 (0.4)	-	1 (0.4)
	Total	24 (9.7)	25 (10.1)	49 (19.8)
Fast growing	Lung cancer (not receiving molecular targeted therapy)	11 (4,5)	61 (24.7)	72 (29.1)
	Metastasis of unknown primary	1 (0.4)	13 (5.3)	14 (5.7)
	Gastric cancer	5 (2)	5 (2)	10 (4)
	Bladder cancer	-	7 (2.8)	7 (2.8)
	Colon cancer	2 (0.8)	2 (0.8)	4 (1.6)
	Rectal cancer	1 (0.4)	2 (0.8)	3 (1.2)
	Hepatocellular carcinoma	-	2 (0.8)	2 (0.8)
	Nasopharyngeal cancer	-	2 (0.8)	2 (0.8)
	Squamous cell carcinoma of skin	-	2 (0.8)	2 (0.8)
	Adenoid cystic carcinoma	1 (0.4)	-	1 (0.4)
	Cholangiocellular carcinoma	-	1 (0.4)	1 (0.4)
	Larynx cancer	-	1 (0.4)	1 (0.4)
	Oncocytic carcinoma	1 (0.4)	-	1 (0.4)
	Pancreatic cancer	-	1 (0.4)	1 (0.4)
	Parotid cancer	-	1 (0.4)	1 (0.4)
	Cervical cancer	1 (0.4)	-	1 (0.4)
	Urothelial carcinoma (extra-bladder)	-	1 (0.4)	1 (0.4)
	Total	23 (9.3)	101 (40.9)	124 (50.2)

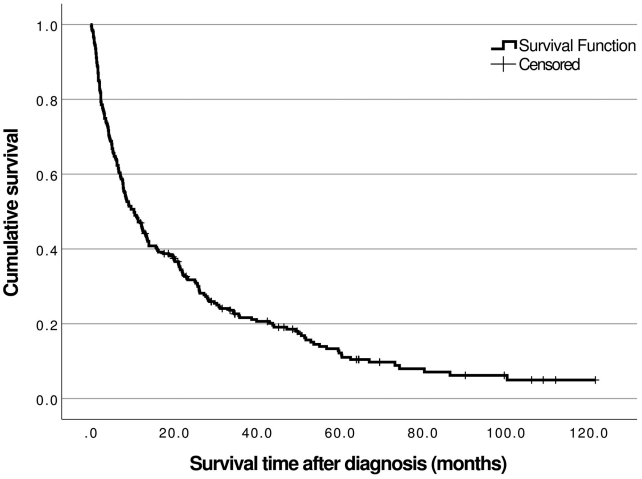

Figure 2. Cumulative survival of patients.

Cancer antigen-125 and C-reactive protein parameters were excluded from multivariate analysis due to the small sample size. Albumin concentration and absolute lymphocyte count were represented as a single PNI value.

As a result of multivariate analysis, low performance scores, low hemoglobin, high white blood cell (WBC) levels, increased lactate dehydrogenase concentration, and decreased PNI score increased the mortality risk. A significantly increased risk was also observed in underweight patients; whereas a reduced risk was observed in obese patients, but this finding was not statistically significant. Growth pattern of the primary tumors was also found to be significant, and it was observed that the mortality risk increased in moderate and fast-growing tumors. There was no increased risk in the LNM group, while a significantly increased risk was observed in those with VBM (Table 4).

Practical applicability and predictive performances were assessed according to the Brier score and AUC values and listed in Table 5. In this context, Janssen and PathFX were sufficient at 1 month, but PathFX performed better at scores. At 3 months, the 2013-Spring, Janssen, PathFX, and SORG models all in acceptable range, and the SORG model achieved higher performance scores. The 2013-Spring,

Table 4. Multivariate analysis results

Variable	Value	HR (95% CI)	*P*
Primary tumor			**<.001**
	Moderate growing	2.003 (1.168-3.437)	**.012**
	Fast growing	3.894(2.495-6.076)	**<.001**
Pathological fracture		1.534 (1.076-2.185)	**.018**
Extraspinal metastasis		1.819 (1.057-3.13)	**.031**
Extraskeletal metastasis			**.012**
	LNM	1.017 (0.648-1.594)	.942
	VBM	1.704 (1.099-2.641)	**.017**
ECOG	2-4	1.705 (1.144-2.54)	**.009**
Hemoglobin	Low	1.511 (1.058-2.158)	**.023**
WBC	High	1.555 (1.069-2.262)	**.021**
LDH	High	2.099 (1.476-2.985)	**<.001**
PNI	Low	1.82 (1.218-2.719)	**.003**
BMI			**.007**
	Underweight	1.617 (1.124-2.326)	**.01**
	Obese	0.795 (0.514-1.23)	.304

Bold values indicate statistical significance.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LNM, lymph node metastases; PNI, prognostic nutritional index; VBM, visceral and/or brain metastases; WBC, white blood cell.

Table 5. Performance scores of prognostic models

Model		1 months	3 months	6 months	12 months	18 months	24 months
Janssen	Brier score	0.192	0.347		0.289		
	AUC value	0.59 (E*)	0.67 (D*)		0.65 (D*)		
2013-Spring	Brier score		0.204	0.229	0.164		
	AUC value		0.76 (C*)	0.77 (C*)	0.83 (B*)		
Original Katagiri	Brier score			0.196	0.204		0.152
	AUC value			0.72 (C*)	0.74 (C*)		0.8 (B*)
Revised Katagiri	Brier score			0.21	0.219		0.162
	AUC value			0.68 (D*)	0.69 (D*)		0.73 (C*)
Pathfx	Brier score	0.124	0.222	0.233	0.208	0.188	0.148
	AUC value	0.64 (D*)	0.64 (D*)	0.68 (D*)	0.73 (C*)	0.72 (C*)	0.75 (C*)
SORG	Brier score		0.15		0.142		
	AUC value		0.83 (B*)		0.87 (B*)		

AUC, area under curve.
*Interpretation of AUC values: A, excellent; B, very good; C, good; D, sufficient; E, bad; F, not useful.

original Katagiri, revised Katagiri, and PathFX models were in the good and sufficient ranges, while the original Katagiri model performed better in terms of score for 6 month predictions. At 12 months, SORG had distinctly good scores among suitable models. Only PathFX estimated survival for 18 months, and it was within a good range. The original Katagiri, revised Katagiri, and PathFX models were graded as good and functional scales for 24 months.

Discussion

There are previous studies about prognostic factors and their effects on the survival of patients with metastatic bone diseases. Unlike other similar studies in the literature, only the carcinoma metastases were included in our study.[8-13,19] Although it is a single-centered retrospective study with numerous parameters, our study has a large sample size and diagnostic variety.

In the high ECOG score group, decreased survival was observed, similar to the literature[8-13] Tumors with moderate and rapid-growth were observed to have increased mortality risk. An increased risk was observed in patients with VBM compared to other groups. These findings were in accordance with the literature[20,21] and used as criteria in all current prognostic models.[8-13,22]

We found that the presence of extraspinal bone metastases posed an increased mortality risk. This finding is supported by Tokuhashi et al[19] and is included as a criterion in their prognostic model.

Pathological fractures had significantly reduced survival in each group, regardless of region. However, no significant difference was observed among regions. This finding shows that pathological fracture in any skeletal part might increase risk, and although it's not supported by many studies,[9,21,23] this parameter was included in PathFX[11] and Janssen[13] models.

The patients with low hemoglobin levels had a significantly higher risk, in parallel with the literature.[11-13,20,21] Survival times were significantly reduced in patients with high WBC counts. The absolute neutrophil and lymphocyte counts or their ratios were previously shown to be prognostic factors.[24] The WBC count is not used frequently in current prognostic models, except SORG.[10] However, Meares et al[21] reported that WBC count was not associated with survival.

The PNI is a marker of both nutritional and inflammatory status.[15] Recently, the prognostic significance of this value in various types of cancer and other diseases has been emphasized, and it was reported that decreased PNI value was associated with reduced survival.[25-28] Similarly, in our study, low PNI values were found to increase mortality risk.

Association of LDH decreasing survival[29] has been demonstrated earlier in the literature and in our study; also a relation with adverse effects on cancer or metastasis was shown.[30]

The risk of mortality was increased in underweight patients in our study in parallel with the literature. However, the prognostic effect of obesity is not fully understood. Some meta-analyses showed that obesity decreased survival in the general population and in patients with breast cancer but increased survival in some other malignancies.[31-34]

No significant difference was found in terms of metastasis burden (solitary or multiple). Although some studies found this finding insignificant in parallel with ours,[21] many studies[9,11-13,20] have shown that multiple bone metastases increased the risk.

Among localizations of the metastases, survival time was increased in patients with axial-only metastasis but decreased in Axial-PLB metastases. Contrary to studies that considered PLB as axial metastases, a significant reduction in survival is observed when PLBs were added to axial skeletal metastases, as in our definition. No significant difference was observed in other groups and the additional DLB group. Similarly, Katagiri et al[9] found no significant difference among anatomical localizations.

Received systemic treatment before, after diagnosis, or during both periods was found to be associated with a higher risk of mortality in univariate analysis. These findings were inconsistent with studies in the literature that have assessed the effect of previous systemic therapy.[8,9,20,21] This contradiction can be interpreted in 2 ways: Firstly, patients could be diagnosed too late for systemic therapy to be effective anymore, or metastasis developed under systemic treatment, indicating the ineffectiveness of systemic therapy.[8] Secondly, as far as we observed in our study, a substantial group of patients could not receive systemic therapy as they died shortly after diagnosis, which could be statistically misinterpreted as premature death caused by a lack of systemic treatment. However, this parameter was found to be insignificant in multivariate analysis.

All of the models included were sufficient in terms of survival prediction according to AUC and Brier scores, but the SORG system obtained distinctly higher performance scores. Our study revealed similar results to a limited number of studies in the literature in terms of the survival prediction of models.[12,21,35-37]

There are some limitations of our study, such as being a retrospective study, shortage of the sample due to the exclusion of patients due to a lack of data, and an inability to compare studies among themselves due to altering samples. We didn't narrow the sample due to the metastatic sites or surgery status, because the variations in these parameters are seen as an advantage, not a limitation. In our opinion, the variation of the diagnoses and metastatic sites increased the accuracy of the applicability of predictive models in real-life clinical practice. In our study, we exclusively focused on predictive models that provide the probability of survival as a percentage at certain time intervals. Although it has been shown to be successful in some other studies;[22,36,37] we chose not to include the OPTIModel system[38] in our research since it provides survival predictions within time intervals.

We think we had the opportunity to observe the applicability of the predictive models in actual clinical practice, which is the primary purpose of these predictive systems. In conclusion, all of the models included in our study were statistically interpreted as applicable in clinical practice and could give an opinion about survival time. However, the newly developed SORG machine learning system made the statistically best predictions in our patient group. Since our patient group represents random clinical practice, we recommend the use of the SORG system for survival prediction.

Ethics Committee Approval: This study was approved by the Ethics Committee of Çukurova University (Approval number: 106; Date: December 4,2020).

Informed Consent: Informed consent was obtained from the patients at the time of surgery or biopsy.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.A.D., A.M., M.A.D.; Design – K.A.D., A.M., M.B., H.S.O.; Supervision – A.M., M.B., M.A.D., H.S.O.; Materials – K.A.D., B.K., M.A.D.; Data Collection and/or Processing – K.A.D., B.K.; Analysis and/or Interpretation – K.A.D., B.K., M.B., M.A.D., H.S.O.; Literature Search – A.M., B.K., M.B.; Writing – K.A.D., A.M., H.S.O.; Critical Review – M.A.D., H.S.O.

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