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Original Article

Development of a Simple Prognostic Risk Score for Patients with Bone Marrow Metastases from Solid Tumors: A Retrospective Cohort Study

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Abstract

Background and objectives: Bone marrow metastasis (BMM) is a rare complication of solid tumors that carries a dismal prognosis. Readily applicable prognostic models for predicting survival in patients with BMM remain limited. This study aimed to identify prognostic factors affecting overall survival in solid tumor patients with BMM and to develop a clinically applicable prognostic risk score.

Materials and methods: Patients with solid tumors who developed BMM during follow up were retrospectively evaluated. Demographic characteristics, primary tumor features, metastatic disease status, hematologic and biochemical parameters, performance status, and antitumor treatments administered after BMM diagnosis were recorded. Overall survival (OS) was defined as the time from the diagnosis of BMM to death or the last follow up. Survival analyses were performed using the Kaplan–Meier method. Prognostic factors were evaluated using Cox proportional hazards regression analyses. A three tier prognostic risk score was established using the variables identified as independent prognostic factors in the multivariable analysis.

Results: A total of 58 patients were included in the study. OS following the diagnosis of BMM was notably poor. In multivariable analysis, de novo metastatic disease and the lack of antitumor therapy following BMM diagnosis were independently associated with inferior overall survival. Based on these two variables, the prognostic risk score stratified patients into low- (0 risk factors), intermediate- (1 risk factor), and high risk (2 risk factors) groups. The median overall survival was 7.8 months in the low risk group, 2.8 months in the intermediate risk group, and 0.5 months in the high risk group. A significant difference in OS was observed among the risk groups (log-rank $p < 0.001$).

Conclusion: In patients with BMM originating from solid tumors, de novo metastatic disease and the lack of antitumor therapy following BMM diagnosis were identified as independent poor prognostic factors. A simple prognostic risk score based on these two variables stratified

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patients into three distinct risk groups with markedly different survival outcomes. External validation studies in larger, independent cohorts are warranted to evaluate the model for clinical implementation.

Introduction

Bone marrow metastasis (BMM) represents an infrequent but severe clinical entity characterized by the dissemination of non hematological malignancies into the bone marrow compartment, signifying advanced disease. Infiltration of the hematopoietic niche by solid tumor cells frequently induces hematological abnormalities, including anemia, thrombocytopenia, leukoerythroblastosis, and, in severe instances, coagulation disorders and microangiopathic hemolytic anemia. Hence, BMM should be kept in mind especially when encountering unexplained cytopenias, a leukoerythroblastic blood profile, or features of microangiopathic hemolytic anemia [1,2]. Moreover, bone marrow evaluation has been documented to serve a vital role in identifying occult primary malignancies [3].

While symptomatic BMM from solid tumors remains an uncommon presentation, it typically portends an unfavorable outcome. Earlier reports have demonstrated that median overall survival (OS) among patients harboring BMM spans merely from a few weeks to several months. Hung and colleagues identified a median OS of 49 days in a cohort of 83 patients, where favorable performance status, prostate cancer, platelet counts exceeding 50,000/μL, and receipt of antitumor therapy correlated with prolonged survival [4]. In another series of 58 patients, Kucukzeybek et al. documented a median OS of 28 days post-BMM diagnosis [5]. However, survival outcomes differ markedly across primary tumor origins, with marrow involvement conferring a particularly grave prognosis in malignancies such as gastric cancer [6].

The clinical course of BMM exhibits marked heterogeneity depending on the primary tumor type and the patient's general performance status. In a study evaluating patients with breast cancer harboring bone marrow involvement, anemia and thrombocytopenia were reported as the most frequent hematological manifestations, with cytopenias improving following systemic therapy in a substantial proportion of patients [7]. Similarly, in a more recent series comprising diverse solid tumors, patients who received antitumor therapy achieved a significantly longer median OS compared with those who did not (11.5 vs. 3.3 months; $p < 0.01$) [8]. These findings suggest that the diagnosis of BMM alone does not entirely dictate patient prognosis, and that treatment feasibility alongside clinical disease characteristics may play pivotal roles in determining survival.

Identifying prognostic factors in patients with BMM is crucial not only for estimating expected survival outcomes but also for individualizing therapeutic decision making. However, a significant proportion of available studies are limited by small sample sizes, single center designs, and cohorts restricted to specific primary tumor types. This limitation hampers the identification of shared prognostic determinants in patients with BMM arising from diverse solid tumors [1,4,5]. Furthermore, heterogeneous findings exist regarding the clinical utility of routine hematological and biochemical parameters in establishing the diagnosis of BMM and in risk assessment [2,3].

A notable contribution in this field is the prognostic scoring study by Chou et al., which encompassed 321 patients with BMM secondary to solid tumors. The Marrow Metastases Prognostic Score (MMPS), developed in a derivation cohort of 165 patients and validated in an independent cohort of 156 patients, incorporated Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor site, platelet count, and the neutrophil to lymphocyte ratio (NLR). This scoring system stratified patients into favorable, intermediate, and poor prognostic groups, demonstrating significant survival discrimination across both cohorts [9]. This study holds particular importance in illustrating that clinical and laboratory variables can be effectively integrated into a straightforward prognostic model for patients with BMM. Nevertheless, exploring alternative risk stratification tools based on fewer variables that

can be readily implemented in routine clinical practice remains of clinical interest.

Therefore, identifying independent clinical and laboratory determinants associated with OS in patients with BMM arising from diverse solid tumors, and integrating these factors into a straightforward prognostic model, represents a clinically meaningful strategy. The objective of the present study was to delineate the independent prognostic factors associated with OS in solid tumor patients who developed BMM, and to construct a simple, clinically feasible prognostic risk score capable of stratifying these patients into distinct risk categories based on their survival outcomes.

Materials and methods

This study was designed as a retrospective cohort study to evaluate the clinical characteristics and prognostic factors associated with OS in patients diagnosed with BMM originating from solid tumors. Patients who presented to the Hematology Outpatient Clinic of Izmir Tepecik Training and Research Hospital between 2015 and 2025, with histopathologically confirmed BMM and accessible clinical, laboratory, and survival data at the time of diagnosis, were included in the study. The study population comprised a total of 58 patients. The diagnosis of BMM was established based on the demonstration of metastatic malignant cells in bone marrow aspiration and/or biopsy specimens. All bone marrow aspiration and trephine biopsy procedures were performed from the posterior superior iliac spine (PSIS) under local anesthesia according to standard hematological protocols. Data regarding demographic characteristics, primary tumor type, stage of disease, pattern of bone marrow involvement, concomitant metastatic sites, ECOG, hematological and biochemical laboratory parameters, and antitumor treatments administered following BMM diagnosis were retrospectively recorded. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Non-Interventional Research Ethics Committee of the University of Health Sciences, İzmir Tepecik Training and Research Hospital (Decision No: 2025/12-08, Date: January 5, 2026). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee. Demographic and baseline clinical characteristics comprised age, gender, ECOG, primary tumor histology, timing of metastasis, marrow infiltration pattern, and concurrent distant metastatic burden. Metastatic status was categorized into de novo metastatic disease versus metachronous/recurrent metastasis arising during clinical follow up. The infiltration pattern in the bone marrow was documented as either focal or diffuse.Laboratory evaluation included hemoglobin, platelet count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, red cell distribution width (RDW), C-reactive protein (CRP), albumin, lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) levels. In addition, the NLR, platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and CRP to albumin ratio (CAR) were calculated as systemic inflammatory and immune response markers. All laboratory parameters were determined based on values obtained closest to the time of BMM diagnosis.The study's primary outcome was OS, calculated in months from BMM confirmation to death or the last documented visit. Surviving patients were censored at their last known follow up date. Patients presenting with locally advanced disease devoid of subsequent distant metastatic recurrence were excluded from comparative analyses between de novo versus metachronous metastatic cohorts.Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were evaluated based on skewness and kurtosis coefficients. Variables with both coefficients within the ± 3 threshold were reported as mean $\pm$ standard deviation, whereas variables with at least one coefficient exceeding these limits were presented as median (minimum–maximum). Categorical variables were expressed as frequencies and percentages [n (%)]. Kaplan–Meier curves were generated to evaluate OS, and between group comparisons were performed via the log-rank test. Median OS with 95% confidence intervals (CIs) was calculated according to the Brookmeyer–Crowley methodology. Univariable Cox proportional hazards regression analysis was initially performed to

determine prognostic factors associated with OS. Continuous laboratory parameters and inflammatory ratios were dichotomized using their respective cohort median values. For albumin, the established cutoff of 3.5 g/dL was applied based on the literature. Variables demonstrating an association at a significance level of $p < 0.20$ in the univariable analysis were incorporated into the multivariable Cox regression model. Tumor type was entered into the model as a categorical variable retaining all of its categories. Results were reported as hazard ratios (HRs), adjusted hazard ratios (aHRs), and 95% CIs. Potential collinearity among covariates was evaluated during the construction of the multivariable model. Because platelet count and the PLR share the same hematological parameter, the risk of multicollinearity arising from their concurrent inclusion was considered. Consequently, platelet count was excluded from the multivariable model, whereas the PLR was retained. A two-sided p-value < 0.05 was considered statistically significant.

Development of the Prognostic Risk Score

The prognostic risk score was constructed based on variables that retained independent prognostic significance for OS in the multivariable Cox regression analysis. Accordingly, two adverse prognostic factors were identified: absence of antitumor therapy following BMM diagnosis and de novo metastatic presentation. Each adverse factor was assigned a score of 1, yielding a total score ranging from 0 to 2 points. Patients were stratified into three risk tiers based on their cumulative scores: low risk (0 points), intermediate risk (1 point), and high risk (2 points). Prognostic discrimination across the stratified risk categories was evaluated via Kaplan–Meier curves and compared using the log-rank test. The clinical validity of the scoring model in relation to OS was established by analyzing median survival estimates and the visual separation of survival trajectories.

Results

Fiftyeight patients were enrolled. The cohort had a mean age of 59.4 ± 14.7 years (range, 17–88 years), comprising 30 males (51.7%) and 28 females (48.3%). An ECOG PS of 0–1 was documented in 43 patients (74.1%), while 15 (25.9%) exhibited an ECOG PS ≥ 2. The predominant primary tumor histologies included breast cancer (34.5%), prostate cancer (19.0%), and neuroendocrine carcinoma (15.5%) [specifically, the primary locations were:

Gastroenteropancreatic tract (GEP-NEC) (n = 5; including pancreas and gastric),

Bronchopulmonary / lung neuroendocrine carcinoma (n = 3), Unknown primary neuroendocrine carcinoma (n = 1)]. Fortythree patients (74.1%) presented with de novo metastatic BMM, whereas 13 (22.4%) had initially locally advanced disease with subsequent metastatic progression during followup (Table 1).

In our cohort of 58 patients: 38 patients (65.5%) received diseasedirected antitumor therapy (palliative systemic chemotherapy, targeted therapy, or endocrine therapy) after the diagnosis of BMM. 20 patients (34.5%) did not receive antitumor therapy and were managed exclusively with best supportive care due to poor performance status, rapid disease deterioration, or profound cytopenias.

BMM exhibited a diffuse pattern in 57 patients (98.3%) and a focal pattern in 1 patient (1.7%). Among concomitant metastatic sites, distant lymph node metastasis (44.8%) and liver metastasis (37.9%) were the most prevalent. Peritoneal and lung metastases were identified in 13.8% and 6.9% of patients, respectively (Table 1).

At the time of BMM diagnosis, the mean hemoglobin level was 8.9 ± 2.2 g/dL. The median neutrophil and lymphocyte counts were 4,200/µL and 1,700/µL, respectively. The mean albumin level was 3.6 ± 0.5 g/dL, whereas the median CRP, LDH, and ALP levels were 33.0 mg/L, 434 U/L, and 229 U/L, respectively.

The median values of the inflammatory/prognostic ratios were 2.3 for NLR, 64.8 for PLR, 3.0 for LMR, and 9.4 for CAR (Table 2).

Univariate Cox regression analysis was performed to determine prognostic factors for OS. Male sex (HR, 1.796; 95% CI, 1.039–3.105; p=0.036), ECOG performance status ≥2 (HR, 6.892; 95% CI, 3.337–14.235; p<0.001), NLR above the median value (HR, 1.814; 95% CI, 1.025–3.213; p=0.041), and high ALP level (HR, 1.773; 95% CI, 1.019–3.086; p=0.043) were associated with a higher risk of death (Table 3).

Table-1: *Sociodemographic and Clinical Characteristics of the Patients*

Variable	n
Age (years), Mean ± SD	59.4 ± 14.7
Sex	
Female, n (%)	28 (48.3)
Male, n (%)	30 (51.7)
ECOG PS	
0-1, n (%)	43 (74.1)
≥2, n (%)	15 (25.9)
Primary tumor type	
Breast, n (%)	20 (34.5)
Prostate, n (%)	11 (19.0)
Neuroendocrin carcinom, n (%)	9 (15.5)
Gastric, n (%)	7 (12.1)
Carcinoma of unknown primary, n (%)	6 (10.3)
Gynecological tumor, n (%)	2 (3.4)
Sarcoma, n (%)	1 (1.7)
NSCLC (Lung), n (%)	1 (1.7)
Biliary tract tumor, n (%)	1 (1.7)
Disease stage at initial diagnosis	
De novo metastasis, n (%)	43 (74.1)
Initially locally advanced, subsequent metastasis, n (%)	13 (22.4)
Locally advanced, n (%)	2 (3.4)
Pattern of bone marrow involvement	
Diffuse, n (%)	57 (98.3)
Focal, n (%)	1 (1.7)
Concomitant metastatic sites (Present), n (%)	
Liver metastasis	22 (37.9)
Lung metastasis	4 (6.9)
Distant lymph node metastasis	26 (44.8)
Peritoneal metastasis	8 (13.8)

Data are presented as n (%) or mean ± standard deviation. ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer. SD: Standart Deviation

Conversely, receiving antitumor therapy after the diagnosis of BMM was significantly associated with a lower risk of death (HR, 0.125; 95% CI, 0.056–0.280; p<0.001). De novo metastatic disease demonstrated a borderline significant association with a higher risk of death (HR, 1.820; 95% CI, 0.991–3.345; p=0.054).

In contrast, RDW above the median value was associated with a lower risk of death in this cohort (HR, 0.444; 95% CI, 0.249–0.794; p=0.006). Tumor type was also significantly associated with overall survival (p<0.001); neuroendocrine carcinoma was associated with a markedly higher risk of death compared to breast cancer (HR, 10.288; 95% CI, 3.907–27.086; p<0.001). Detailed results for the remaining variables are presented in Table 3.

The pattern of bone marrow involvement was not significantly associated with survival. As focal involvement was observed in only one patient, the confidence interval for this comparison was wide, and the result was considered descriptive (HR, 2.595; 95% CI, 0.346–19.448; p=0.354) (Table 3).

Table-2: *Hematologic and Biochemical Parameters and Inflammatory Ratios of the Patients*

Parameter	Metric	n
Hemoglobin (g/dL)	Mean ± SD	8.9 ± 2.2
Platelet (/uL)	Mean ± SD	151190.3 ± 157907.9
Neutrophils (/uL)	Median (Min–Max)	4200.0 (220.0-19700.0)
Lymphocytes (/uL)	Median (Min–Max)	1700.0 (300.0-32600.0)
Monocytes (/uL)	Mean ± SD	467.5 ± 318.1
RDW (%)	Median (Min–Max)	17.3 (12.6-29.0)
CRP (mg/L)	Median (Min–Max)	32 (0.7-242.0)
Albumin (g/dL)	Mean ± SD	3.6 ± 0.5
LDH (U/L)	Median (Min–Max)	437 (128.0-3268.0)
ALP (U/L)	Median (Min–Max)	240 (45.0-1688.0)
NLR	Median (Min–Max)	2.39 (0.1-43.0)
PLR	Median (Min–Max)	68.67 (0.0-1046.7)
LMR	Median (Min–Max)	3.0 (1.0-232.9)
CAR	Median (Min–Max)	9.35 (0.2-71.2)

RDW = Red cell distribution width; LDH = Lactate dehydrogenase; ALP = Alkaline phosphatase; NLR = Neutrophil-to-lymphocyte ratio; PLR = Platelet-to-lymphocyte ratio; LMR = Lymphocyte-to-monocyte ratio; CAR = C-reactive protein-to-albumin ratio.

Variables demonstrating an association at the p < 0.20 level in the univariate analysis were included in the multivariable Cox regression model. To minimize potential collinearity, platelet count was excluded from the model and PLR was retained, as both share the same hematologic parameter.

In the multivariable analysis, two variables remained independent prognostic factors for OS. Receiving antitumor therapy following the diagnosis of BMM was associated with a lower risk of death (adjusted HR, 0.070; 95% CI, 0.015–0.324; p<0.001). Conversely, de novo metastatic disease was independently associated with an increased risk of death (adjusted HR, 2.329; 95% CI, 1.161–4.673; p=0.017) (Table 4; Figure 1).

Elevated NLR, which was found to be significant in the univariate analysis, did not reach statistical significance in the multivariable analysis (adjusted HR, 2.275; 95% CI, 0.951–5.443; p=0.065). Similarly, neuroendocrine carcinoma histology was not confirmed as an independent prognostic factor in the multivariable model (adjusted HR, 2.828; 95% CI, 0.815–9.813; p=0.101). Other clinical and laboratory variables were also not statistically significant in the multivariable model (Table 4).

The multivariable model was statistically significant overall (likelihood ratio $\chi^2 = 56.26$, df = 15, p < 0.001) (Figure 1).

Development of the Prognostic Risk Score

A simple prognostic risk score was constructed using the two variables identified as independent prognostic factors in the multivariable Cox regression analysis. De novo metastatic disease and the absence of antitumor therapy following the diagnosis of BMM were defined as adverse prognostic factors, with 1 point assigned to each factor. Consequently, the total score ranged from 0 to 2. Based on their scores, patients were stratified into three risk groups: low risk (0 points), intermediate risk (1 point), and high risk (2 points) (Table 5).

Table-3: *Results of Univariate Cox Regression Analysis for Overall Survival*

Variable	HR	95% CI	p
Age (years, continuous)	1.003	0.984-1.022	p = 0.763
Hemoglobin (g/dL, continuous)	1,056	0,918-1,214	p = 0,448
Sex: Male (ref: Female)	1,796	1,039-3,105	p = 0,036
ECOG ≥2 (ref: 0–1)	6,892	3,337-14,235	p < 0,001
Bone marrow involvement pattern: Focal (ref: Diffuse)	2,595	0,346-19,448	p = 0,354
Liver metastasis: Yes (ref: No)	1,292	0,748-2,232	p = 0,357
Treatment received: Yes (ref: No)	0,125	0,056-0,280	p < 0,001
De novo metastasis: Yes (ref: Recurrent)	1,820	0,991-3,345	p = 0,054
Albumin < 3.5 g/dL (ref: ≥3.5)	1,022	0,580-1,804	p = 0,939
Neutrophils ≥ median (4200/µL)	1,364	0,794-2,343	p = 0,260
Lymphocytes < median (1700/µL)	0,712	0,409-1,239	p = 0,229
Monocytes ≥ median (400/µL)	0,998	0,576-1,730	p = 0,995
RDW ≥ median (%17.3)	0,444	0,249-0,794	p = 0,006
ALP ≥ median (240 U/L)	1,773	1,019-3,086	p = 0,043
Platelet <median (70000)	1,506	0,875-2,592	p = 0,139
LDH ≥ median (437)	1,437	0,838-2,465	p = 0,188
CRP ≥ median (32.0)	1,694	0,975-2,942	p = 0,061
NLR ≥ median (2.39)	1,814	1,025-3,213	p = 0,041
PLR ≥ median (68.67)	0,622	0,361-1,072	p = 0,087
LMR <median (3.00)	1,441	0,834-2,491	p = 0,191
CAR ≥ median (9.35)	1,397	0,811-2,408	p = 0,229
Tumor type: Prostate (ref: Breast)	1,407	0,650-3,047	p = 0,387
Tumor type: Neuroendocrine carcinoma (ref: Breast)	10,288	3,907-27,086	p < 0,001
Tumor type: Gastric (ref: Breast)	2,770	1,074-7,146	p = 0,035
Tumor type: Other (ref: Breast)	4,551	1,908-10,854	p < 0,001

Hazard ratios (HR) and 95% confidence intervals (95% CI) are presented from the Cox regression analysis. Reference categories for categorical variables are indicated in parentheses. Continuous laboratory parameters and inflammatory ratios were categorized based on the cohort median value of each respective variable. A cut-off value of 3.5 g/dL was used for albumin. Breast cancer served as the reference category for tumor type.

Abbreviations: *RDW, red blood cell distribution width; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein-to-albumin ratio; ECOG, Eastern Cooperative Oncology Group.*

Table-4: *Results of Multivariable Cox Regression Analysis for OS*

Variables	Adjusted HR	95% CI	p
Male sex (ref: Female)	1.525	0.591-3.937	p = 0.383
ECOG ≥ 2 (ref: 0–1)	1.912	0.441-8.291	p = 0.386
Treatment: Yes (ref: No)	0.070	0.015-0.324	p < 0.001
De novo metastatic disease (reference: Recurrent)	2.329	1.161-4.673	p = 0.017
RDW ≥ median (ref: < median)	1.274	0.574-2.829	p = 0.552
ALP ≥ median (ref: < median)	1.667	0.758-3.666	p = 0.204
LDH ≥ median (ref: < median)	1.774	0.774-4.065	p = 0.175
CRP ≥ median (ref: < median)	0.730	0.311-1.714	p = 0.471
NLR ≥ median (ref: < median)	2.275	0.951-5.443	p = 0.065
PLR ≥ median (ref: < median)	0.687	0.309-1.527	p = 0.357
LMR <median (ref:: ≥ median)	1.679	0.828-3.402	p = 0.151
Tumor type: Prostate (ref: Breast)	0.551	0.153-1.983	p = 0.362
Tumor type: Neuroendocrine carcinoma (ref: Breast)	2.828	0.815-9.813	p = 0.101
Tumor type: Gastric (ref: Breast)	0.992	0.301-3.270	p = 0.989
Tumor type: Other (ref: Breast)	0.436	0.109-1.748	p = 0.241

Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) from the multivariable Cox regression analysis are presented. Variables with p < 0.20 in the univariate analysis were included in the model. Reference categories for categorical variables are indicated in parentheses. Due to potential collinearity between platelet count and PLR, the platelet variable was excluded from the multivariable model. Breast cancer served as the reference category for tumor type.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RDW, red blood cell distribution width; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

Figure 1. Forest plot of the multivariable Cox regression model for overall survival.

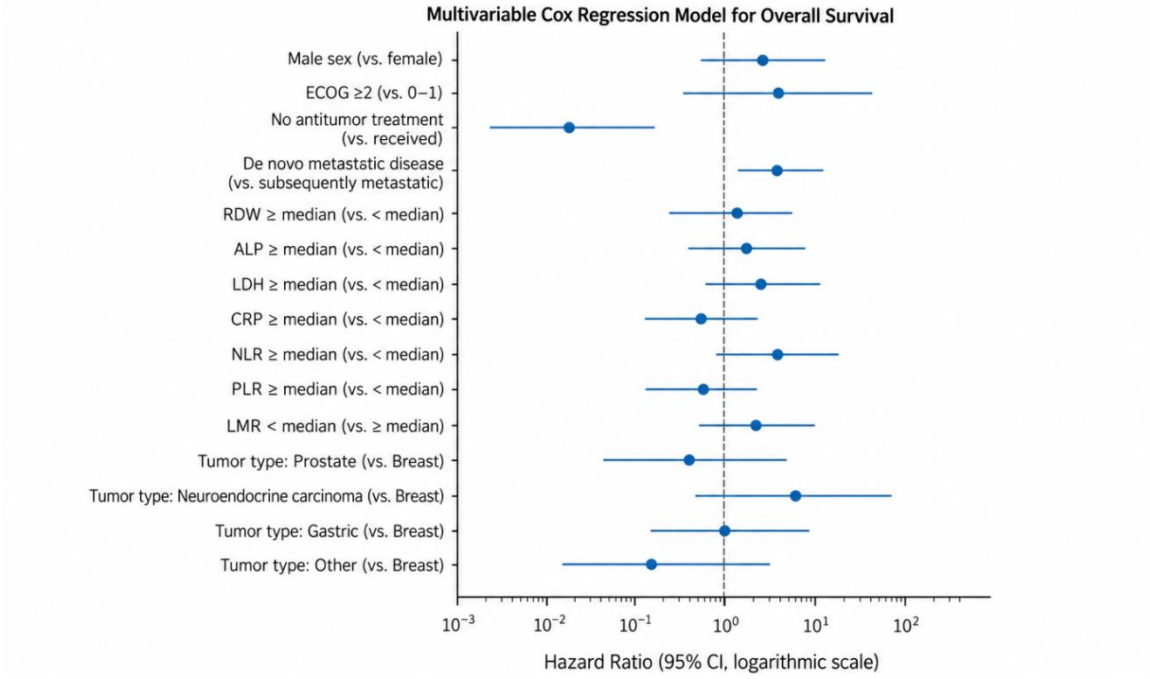


Table-5: *Comparison of OS by Prognostic Risk Group*

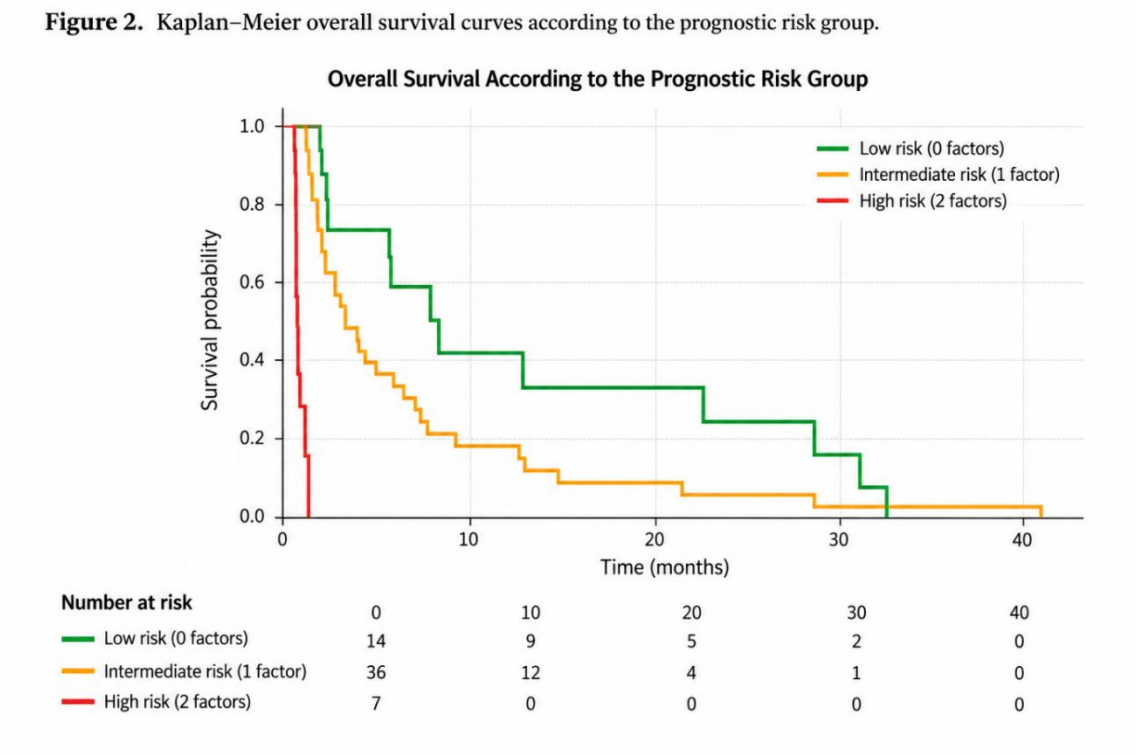
Prognostic risk group	Median OS (months)	Median OS 95% CI
Low risk (0 factors)	7.8	7.8 (1.7-25.5)
Intermediate risk (1 factor)	2.8	2.8 (1.6-5.5)
High risk (2 factors)	0.5	0.5 (0.3-1.0)

Log-rank χ^2 = 63.14, df = 2, p < 0.001. The 95% confidence interval for median OS was calculated using the Brookmeyer–Crowley method

In the low risk group (n = 14), median OS was 7.8 months (95% CI, 1.7–25.5), compared with 2.8 months (95% CI, 1.6–5.5) in the intermediate risk group (n = 36) and only 0.5 months (95% CI, 0.3–1.0) in the high risk group (n = 7) (Table 5).

A distinct and highly statistically significant difference in OS was observed among the risk groups (log-rank χ^2 = 63.14, df = 2, p < 0.001). Kaplan–Meier analysis demonstrated a clear separation of the survival curves across the risk groups (Figure 2). Furthermore, the stepwise decline in median OS from 7.8 to 2.8 months and subsequently to 0.5 months with increasing risk score demonstrated a strong gradient relationship between the score and survival outcomes (Table 5; Figure 2).

Figure 2. Kaplan–Meier overall survival curves according to the prognostic risk group.



Discussion

In this retrospective study, we identified two independent factors associated with OS in patients with BMM from solid tumors: de novo metastatic disease and the lack of antitumor therapy following BMM diagnosis. A simple prognostic risk score derived from these two variables stratified patients into three distinct groups: low, intermediate, and high risk. Median OS decreased stepwise from 7.8 months in patients with no risk factors to 2.8

months in those with one risk factor, and down to 0.5 months in those with two risk factors (log-rank $p < 0.001$). These findings suggest that, despite the heterogeneous nature of primary tumors associated with BMM, a limited number of readily available clinical variables can provide clinically meaningful prognostic discrimination.

BMM is an infrequent yet particularly aggressive manifestation of advanced solid malignancies. Although previous studies have documented markedly dismal survival outcomes following the diagnosis of BMM, prognosis has been shown to vary substantially depending on primary tumor type, performance status, hematologic derangements, and the feasibility of administering antitumor therapy [4,5]. The biological and clinical complexity of BMM has also been highlighted in recent comprehensive reviews, which detail the reciprocal interactions between circulating tumor cells and the bone marrow microenvironment, as well as the profound hematologic consequences of diffuse marrow infiltration [10].

In our study, de novo metastatic disease was independently associated with worse OS. Patients presenting with metastatic disease at the time of initial cancer diagnosis had more than a two fold increased risk of death compared to those who developed metachronous metastases. Although the underlying biological mechanism cannot be definitively established due to the retrospective design, de novo metastatic presentation may reflect a more aggressive tumor biology, a higher initial disease burden, or early hematogenous dissemination. In particular, the timing and pattern of metastatic spread may provide prognostic insights extending beyond the mere anatomical presence of BMM.

The second independent prognostic factor identified in our study was the administration of antitumor therapy following the diagnosis of BMM. Patients who received antitumor therapy exhibited significantly longer survival compared to those who did not. This finding is consistent with a recent study evaluating solid tumor patients with BMM, which reported a median OS of 11.5 months in patients receiving antitumor therapy versus 3.3 months in untreated patients [11]. Similarly, the association between active treatment and prolonged survival has been demonstrated in other BMM cohorts, suggesting that carefully selected patients with an adequate clinical performance status may derive meaningful benefit from disease directed therapy.

More recent data also corroborate the prognostic relevance of treatment feasibility. In a retrospective study evaluating 41 solid tumor patients with bone marrow involvement, although the median OS for the entire cohort was merely 23 days, patients receiving antitumor therapy had a significantly longer median survival than those managed with supportive care alone (158 vs. 13 days; $p < 0.001$) [12]. These findings are broadly consistent with our results and support the notion that the ability to tolerate active treatment serves as a critical determinant of clinical outcomes in patients with BMM.

However, the association between treatment and survival must be interpreted with caution. The decision to initiate therapy following a BMM diagnosis is not randomized; rather, it is heavily influenced by performance status, organ function, hematologic reserve, disease burden, symptomatology, and the clinician's overall clinical judgment. Treatment status may therefore reflect patient fitness and baseline eligibility rather than solely the therapeutic efficacy of antitumor agents. Furthermore, an earlier study of 30 patients with BMM reported significantly prolonged survival in those who received systemic therapy compared with those receiving supportive care alone, underscoring the strong interplay between treatment fitness and clinical outcomes [13].

The prognostic role of systemic inflammation was also evaluated in our study. Although the NLR was associated with OS in the univariate analysis, it lost independent significance following multivariable analysis. This finding should not be interpreted as an absence of prognostic relevance for NLR in cancer. In an umbrella review evaluating systematic reviews and meta analyses, elevated NLR was consistently associated with poorer outcomes across numerous malignancies, though the strength of this association varied according to tumor type and clinical setting [14]. In our cohort, the loss of significance after multivariable adjustment may be attributable to the limited sample size, the

heterogeneity of primary tumors, and the collinear overlap of inflammatory parameters with other indicators of disease severity.

Similarly, various laboratory variables—including ALP, LDH, and RDW—were associated with survival in univariate analyses but failed to retain independent prognostic significance in the final model. This may be related to the unique biological characteristics of BMM. In this setting, hematologic and biochemical derangements often arise from multiple convergent processes, such as marrow infiltration, systemic inflammation, high tumor burden, organ dysfunction, and widespread metastatic dissemination. Consequently, while individual laboratory parameters harbor prognostic value, their independent contributions may become less pronounced when major clinical variables are evaluated concurrently.

A notable finding of our study is the development of a simple, two factor prognostic risk score. The previously established and independently validated Marrow Metastases Prognostic Score (MMPS) incorporates ECOG performance status, primary tumor site, platelet count, and NLR [9]. The MMPS successfully stratified patients into good, intermediate, and poor prognostic groups with distinctly divergent median survivals in both the development and validation cohorts. In contrast to the MMPS, our model relies on only two readily accessible clinical variables: de novo metastatic presentation and the omission of antitumor therapy following BMM diagnosis. Consequently, the present model should be viewed not as a replacement for the MMPS, but rather as a simplified alternative approach.

The primary clinical appeal of our score lies in its simplicity. One point is assigned to each adverse factor, yielding a total score ranging from 0 to 2. In our cohort, this straightforward classification established a distinct survival gradient, with median OS dropping from 7.8 months in the low risk group to 2.8 months in the intermediate risk group, and to just 0.5 months in the high risk group. Such an easily applicable stratification tool may prove particularly useful in routine clinical practice, where rapid decision making regarding treatment intensity, supportive and palliative care allocation, and prognostic communication is essential.

Nevertheless, the proposed score should be considered exploratory. This study was conducted in a relatively small cohort, and the model was both developed and evaluated within the same patient population. Consequently, the observed discrimination among risk groups may overestimate its predictive performance in independent cohorts. Current guidelines for prognostic prediction models emphasize transparent reporting across model development, variable selection, outcome definition, predictive performance, and validation processes [15]. Therefore, external validation in independent cohorts is mandatory before this risk score can be adopted into routine clinical practice.

The relatively small sample size of our study represents another notable limitation. Although the final risk score comprises only two variables, the initial multivariable Cox model included a relatively large number of candidate parameters compared to the number of patients and observed events. Methodological principles in prognostic modeling emphasize that adequate sample size must be evaluated not merely by total patient count, but critically in relation to the number of events and candidate predictors evaluated; an insufficient event to variable ratio can lead to model overfitting and unstable risk estimates [16]. Consequently, the current scoring system should be regarded as a preliminary prognostic framework that warrants validation in larger multicenter cohorts.

A particularly critical methodological issue is the inclusion of antitumor therapy administered after BMM diagnosis as one of the two components of the risk score. Because treatment is initiated following the diagnosis of BMM and may occur at varying time points during followup, patients classified as having received therapy inherently had to survive long enough to receive it. Overlooking the time-dependent nature of treatment exposure can introduce immortaltime bias, thereby potentially inflating the apparent survival advantage attributed to antitumor therapy [17].

This issue is particularly relevant to the strong association between treatment receipt and survival observed in our study. Consequently, the present analysis should not be interpreted as establishing a causal treatment effect. Instead, receiving therapy likely reflects both therapeutic exposure and the

patient's baseline clinical fitness to tolerate intervention. In observational studies, patients who survive longer naturally have greater opportunities to receive therapy, whereas those who succumb early are invariably categorized as untreated, introducing survivor treatment bias [18]. To mitigate this limitation, future studies should model treatment exposure as a time dependent covariate or implement an appropriate landmark analysis.

Our study has several additional limitations. First, its retrospective design inherently carries the potential for selection and information bias. Second, the inclusion of diverse primary tumor histologies within a single cohort may have contributed to outcome heterogeneity due to inherent differences in tumor biology and treatment responsiveness. Third, the relatively modest sample size limited the statistical precision of subgroup analyses. Fourth, the proposed prognostic score has not yet undergone external validation. Fifth, from a diagnostic perspective, bone marrow aspiration alone may yield non-diagnostic or hemodiluted samples ('dry tap') in the presence of extensive marrow necrosis, desmoplasia, or dense tumor cell packing. The concurrent performance of a trephine core biopsy with immunohistochemical staining remains crucial to enhance diagnostic yield, prevent false-negative aspirates, and accurately evaluate the extent of marrow infiltration by solid malignancies. These limitations are particularly pertinent given the substantial biological and clinical heterogeneity of patients with BMM arising from distinct primary malignancies.

Nevertheless, our study has several clinically important strengths. BMM is an uncommon clinical entity, and most available literature is derived from relatively small retrospective cohorts. Rather than merely describing the clinical characteristics of BMM, our study specifically focused on prognostic risk stratification. More importantly, the proposed score relies on readily accessible clinical variables that do not require specialized molecular testing or complex computational algorithms. The distinct survival separation observed across the three risk categories supports the further investigation of this pragmatic approach in future studies.

Future multicenter studies should validate the proposed score in larger and more diverse patient populations. Ideally, such investigations should directly compare its prognostic performance against the previously established MMPS, evaluate both discrimination and calibration metrics, and account for the time-dependent nature of treatment exposure. Upon successful external validation, this simple two-factor score could complement existing prognostic tools and assist clinicians in identifying patients with particularly limited life expectancy following a diagnosis of BMM.

Conclusion

In summary, our study demonstrates that de novo metastatic presentation and the omission of antitumor therapy following the diagnosis of BMM are independently associated with poor overall survival in patients with solid tumor related BMM. A simple, two factor prognostic score based on these variables stratified patients into low, intermediate, and high risk categories with markedly distinct survival outcomes. The simplicity of this model and its reliance on readily available clinical variables may facilitate pragmatic prognostic assessment in this rare and clinically challenging patient population. Nonetheless, given the retrospective design, small sample size, potential treatment related immortal time bias, heterogeneity of primary tumors, and lack of external validation, this score should currently be considered exploratory and hypothesis generating. Larger multicenter studies are warranted to validate its prognostic utility.

Conflict of interest

The authors declare that they have no competing interests, either financial or non-financial, related to the work presented in this manuscript.

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Authors' Contributions

SG conceptualized and designed the study, performed the statistical analyses, and drafted the original manuscript. MU supervised the research, managed data collection and curation, and critically revised the manuscript for important intellectual content. MCU contributed to data acquisition, formal analysis, and interpretation of clinical and pathological data. BBC assisted in data collection, literature review, and manuscript preparation. All authors read and approved the final version of the manuscript.

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