Original Article

Serum alkaline phosphatase is a prognostic marker in bone metastatic disease of the extremity

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ARTICLE INFO

Keywords:

Alkaline phosphatase
Bone metastasis
Survival
Prognostic factor
Biomarker

ABSTRACT

Purpose: The purpose of this study was to determine the prognostic value of serum alkaline phosphatase for treatment decision making in metastatic bone disease.

Methods: 1090 patients who underwent surgery for extremity metastatic disease were retrospectively identified at two tertiary care centers. The association between alkaline phosphatase and mortality was assessed by bivariate and multivariate analyses.

Results: Three-month and one-year mortality rates were 305 (29%) and 639 (62%), respectively. Alkaline phosphatase was associated with mortality at both three months and one year.

Conclusion: Serum alkaline phosphatase may be a useful marker in prognostic algorithms for patients with extremity metastatic disease.

1. Introduction

1.1. Background

Metastatic bone disease is the third most common site of metastasis in cancer patients.¹ Especially in patients with lung, breast, or prostate cancer skeletal metastases frequently occur.^{1,2} Skeletal metastases limit mobility, cause pain, lead to pathologic fractures, and decrease quality of life significantly.³ Decision making on the appropriateness of surgical management in this population is partly dependent on the preoperative estimations of expected survival.¹ Several prognostic factors have previously been identified and multiple prognostic models have been created to improve decision making.^{4–6} In a recently developed machine learning model for the same purpose, alkaline phosphatase was selected by random forest algorithms as a predictor.⁷ The aim of the current study was to shed more light on its utility as a prognostic marker in patients with extremity metastatic bone disease.

1.2. Rationale

Serum alkaline phosphatase is released by both liver and bone.

Elevated serum alkaline phosphatase can be the result of increased osteoblastic activity in bone disease and/or increased synthesis by hepatocytes in liver disease.^{8,9} These mechanisms suggest that serum alkaline phosphatase may be a useful marker for metastatic burden and a prognostic marker for survival in patients with extremity metastatic bone disease.

1.3. Purpose of the study

The purpose of this retrospective cohort study was to investigate the value of serum alkaline phosphatase in the prognostication of patients with metastatic disease of the extremities. Specifically, we examined the association of this marker with three-month and one-year mortality in this population. Additionally, we sought to determine the relationship between serum alkaline phosphatase and baseline metastatic tumor burden.

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<https://doi.org/10.1016/j.jor.2020.08.008>

Received 11 May 2020; Accepted 11 August 2020

Available online 17 August 2020

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2. Methods

2.1. Study design and setting

The current study was carried out according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.¹⁰ Our institutional review board approved the study. Retrospective review at two tertiary care centers was used to identify patients with who underwent surgical management for extremity metastatic bone disease.

2.2. Participants/study subjects

The following inclusion criteria were used to identify eligible patients: (1) 18 years or older, (2) surgical management for metastatic long bone disease, (3) date of surgery between January 1999 and January 2017. Surgical management included the following operations: endo-prosthetic reconstruction, plate-screw fixation, intramedullary nailing and dynamic hip screw. Only the first surgery per patient was included, if patients underwent more than one operation on different occasions to prevent the violation of the statistical assumption of independence. Patients that did not receive their original treatment at one of the two centers were excluded. Overall, 1090 patients were identified with three-month and one-year mortality rates were of 29% (n = 305) and 62% (n = 639), respectively. The majority of patients was female (56% versus 44%) and most were under the age of 65 (55%).

2.3. Outcome

The primary outcome was overall survival after surgery and the date of death was obtained from clinical documentation in electronic medical records and/or the Social Security Death Index.¹¹

2.4. Covariates

The following demographic variables were extracted: sex, age, body mass index (kg/m²), and any other Charlson comorbidity in addition to metastatic cancer. Disease factors that were collected were: primary tumor histology in the groupings proposed by Katagiri et al.⁴ [slow growth, moderate growth, rapid growth]. Additional factors were anatomic location [lower extremity, upper extremity], presence of multiple bone metastases (defined as metastatic bone foci at other sites than the primary operative site), spine metastases, visceral metastases (defined as lung and or liver metastases), brain metastases, previous systemic therapy, and prior local radiation to the affected long bone. Preoperative laboratory values that were collected were hemoglobin (g/dL), platelet count (x10³/μL), white blood cell count (x10³/μL), creatinine (mg/dL), calcium (mg/dL), platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, preoperative albumin (g/dL), and alkaline phosphatase (IU/L).

2.5. Statistical analysis

For baseline characteristics, categories are displayed as frequencies and percentages. The optimal cutoff value of serum alkaline phosphatase was determined using López-Ratón et al.'s optimal cutpoint method with the area under the receiver operating curve metric.¹²

Bivariate analyses for serum alkaline phosphatase with baseline characteristics and outcomes were performed with univariable logistic regression. Boxplots were created to visualize the association between elevated serum alkaline phosphatase and metastatic burden and Kaplan-Meier curves were generated to visualize the association between serum alkaline phosphatase and survival up to one year. Multiple imputation was used for variables with less than 30% missing data.¹³ Multivariable logistic regression with bootstrapped (100 replications with replacement) backward stepwise elimination was used to determine whether

serum alkaline phosphatase was associated with three-month and one-year mortality.

The confidence intervals given are 95% confidence intervals and p-values <0.05 were deemed significant.

3. Results

3.1. Alkaline phosphatase and baseline characteristics

Baseline characteristics are displayed in Table 1. Fig. 1 shows the boxplots of alkaline phosphatase with metastatic burden. Serum alkaline phosphatase was associated with [A] other bone metastasis (p < 0.001), [B] spinal metastasis (p < 0.001), and [C] visceral metastasis (p < 0.001) but not [D] brain metastasis (p = 0.2). The optimal cutoff for alkaline phosphatase was determined to be 100 IU/L using the area under the receiver operating curve metric. Table 2 shows the association of serum alkaline phosphatase with baseline characteristics after being dichotomized at this threshold. Factors associated with this marker included older age (p = 0.04), local radiation (0.001), hemoglobin (p =

Table 1
Baseline characteristics of the study population (n = 1090).

Variable	Category	Number (%)
Sex	Female	610 (56.0)
	Male	480 (44.0)
Age (years)	<65	595 (54.6)
	≥65	495 (45.4)
BMI (kg/m ²)	<18	21 (1.9)
	>30	223 (20.5)
	18–30	609 (55.9)
	Unknown	237 (21.7)
Additional comorbidity	No	501 (46.0)
	Yes	584 (53.6)
	Unknown	5 (0.5)
Primary tumor	Slow growth	460 (42.2)
	Moderate growth	263 (24.1)
	Rapid growth	367 (33.7)
Anatomical location	Lower extremity	835 (76.6)
	Upper extremity	255 (23.4)
Other bone metastases		845 (77.5)
Spine metastases		626 (57.4)
Visceral metastases		487 (44.7)
Brain metastases		175 (16.1)
Previous systemic therapy		676 (62.0)
Prior local radiation to affected long bone		194 (17.8)
Hemoglobin (g/dL)	≤10	236 (21.7)
	>10	708 (65.0)
	Unknown	146 (13.4)
Platelets (x10 ³ /μL)	150–450	136 (12.5)
	<150	73 (6.7)
	>450	735 (67.4)
White Blood Cell Count (x10 ³ /μL)	Unknown	146 (13.4)
	<11	773 (70.9)
	≥11	171 (15.7)
Creatinine (mg/dL)	Unknown	146 (13.4)
	<1	615 (56.4)
	≥1.0	309 (28.3)
Calcium (mg/dL)	Unknown	166 (15.2)
	<9	326 (29.9)
	≥9	564 (51.7)
Platelet-to-lymphocyte ratio	Unknown	200 (18.3)
	<408	429 (39.4)
	≥408	334 (30.6)
Neutrophil-to-lymphocyte ratio	Unknown	327 (30.0)
	<4.7	340 (31.2)
	≥4.7	424 (38.9)
Albumin (g/dL)	Unknown	326 (29.9)
	<3.8	432 (39.6)
	≥3.8	338 (31.0)
Alkaline phosphatase (IU/L)	Unknown	320 (29.4)
	<100	372 (34.1)
	≥100	402 (36.9)
	Unknown	316 (29.0)

Fig. 1. Serum alkaline phosphatase was associated with preoperative presence of A) other bone metastasis ($p < 0.001$), B) spine metastasis ($p < 0.001$), and C) visceral metastasis ($p < 0.001$). It was not associated with D) brain metastasis ($p = 0.2$).

0.04), creatinine ($p = 0.002$), platelet-to-lymphocyte ratio ($p = 0.04$), and albumin ($p < 0.001$).

3.2. Alkaline phosphatase and survival

For patients with serum alkaline phosphatase below the threshold of 100 IU/L, three-month and one-year mortality rates were 23% ($n = 84$) and 55% ($n = 196$), respectively. In comparison, for patients with elevated serum alkaline phosphatase, three-month and one-year mortality rates were 39% ($n = 148$) and 74% ($n = 281$) respectively. Fig. 2 shows the Kaplan-Meier predicted survival curves by strata of serum alkaline phosphatase; elevated serum alkaline phosphatase was associated with lower survival at all time points up to one year. In bivariate analysis, elevated alkaline phosphatase was associated with three-month (Odds ratio [OR] = 1.6, 95% confidence interval [CI] = 1.2–2.1) and one-year (OR = 1.6, CI = 1.3–2.1) mortality. On multivariate analysis, serum alkaline phosphatase remained associated with three-month (OR = 1.5, CI = 1.1–2.1), and one-year (OR = 1.5, CI = 1.1–2.0) mortality (Tables 3 and 4).

4. Discussion

4.1. Summary

Serum alkaline phosphatase is associated with baseline metastatic tumor burden (visceral metastasis, multiple bone metastases, and spine metastasis) in cancer patients undergoing surgical management for extremity metastatic bone disease. Elevated preoperative serum alkaline phosphatase is an independent prognostic marker for ninety-day and one-year survival in this population.

4.2. Alkaline phosphatase and metastatic disease

Alkaline phosphatase has previously been identified as a marker for the presence of liver and bone metastases in different types of cancer, including breast cancer,¹⁴ lung cancer,¹⁵ and bladder cancer.¹⁶ Chen et al. studied 2133 patients with breast cancer of which 327 (15%) had bone metastases. They found high alkaline phosphatase to be an independent risk factor for the development of a bone metastasis.¹⁴ Zhou et al. studied a total of 2021 patients with lung cancer of whom 483

Table 2

Bivariate analyses of elevated alkaline phosphatase with baseline characteristics (n = 1090).

Variable	Category	OR	95% CI	p-value
Age years	≥65	0.77	0.60–0.99	0.04
Male sex	-	0.92	0.71–1.18	0.5
BMI kg/m ²	18–30	reference	-	-
	<18	1.38	0.53–3.57	0.5
	>30	0.97	0.73–1.30	0.86
Additional comorbidity	-	0.94	0.73–1.20	0.61
Primary tumor	Slow growth	reference	-	-
	Moderate growth	1.08	0.78–1.49	0.65
	Rapid growth	1.03	0.77–1.37	0.83
Lower Extremity Location	-	0.93	0.69–1.26	0.65
Other Bone Metastasis	-	1.49	1.11–1.99	0.008
Spine Metastasis	-	1.61	1.25–2.07	<0.001
Visceral Metastasis	-	1.24	0.97–1.60	0.09
Brain Metastasis	-	0.91	0.65–1.27	0.57
Previous Systemic Therapy	-	1.2	0.93–1.55	0.16
Local Radiation	-	0.59	0.43–0.81	0.001
Hemoglobin g/dL	≤10	1.36	1.01–1.83	0.04
Platelets x10 ³ /uL	150–450	reference	-	-
	<150	1.06	0.74–1.51	0.77
	>450	1.15	0.72–1.84	0.56
WBC ×10 ³ /uL	>11	1.03	0.74–1.44	0.84
Creatinine mg/dL	≥1.0	0.66	0.50–0.85	0.002
Calcium mg/dL	≥9.0	1.08	0.83–1.40	0.56
Platelet-to-lymphocyte ratio	≥408	1.32	1.01–1.74	0.04
Neutrophil-to-lymphocyte ratio	≥4.7	1.08	0.84–1.39	0.55
Albumin	<3.8	2.97	2.27–3.88	<0.001
Outcomes				
Three-month mortality	-	1.61	1.21–2.14	0.001
One-year mortality	-	1.62	1.25–2.09	<0.001

(24%) had bone metastasis. Elevated alkaline phosphatase was found to be independently associated with bone metastasis in this patient group.¹⁵

4.3. Alkaline phosphatase and survival in metastatic cancer

Previous studies have found elevated alkaline phosphatase to be a prognostic marker for poorer survival in metastatic cancer.^{17–20} A study consisting of 1790 patients with spinal metastatic disease from the National Surgical Quality Improvement Program (NSQIP) found an elevated alkaline phosphatase as a marker for thirty-day mortality on multivariable analysis.¹⁹ Another study consisting of 732 patients with spinal metastatic disease confirmed those findings for ninety-day and one-year survival.¹⁸

Table 3

Multivariate analysis of three-month mortality (n = 1090).

Variable	Category	OR	95% CI	p-value
Three-month mortality				
Age years	≥65	1.49	1.07–2.07	0.02
BMI kg/m ²	18–30	reference	-	-
	<18	2.92	0.97–8.76	0.06
	>30	0.83	0.56–1.23	0.35
Additional comorbidity	-	1.37	0.99–1.91	0.06
Primary tumor	Slow growth	reference	-	-
	Moderate growth	2.12	1.36–3.30	<0.001
	Rapid growth	5.49	3.64–8.27	<0.001
Spine metastases	-	1.37	0.97–1.92	0.07
Visceral metastases	-	1.43	1.01–2.04	0.05
Brain metastases	-	1.71	1.11–2.64	0.01
Hemoglobin g/dL	≤10	2.73	1.89–3.93	<0.001
Platelets x10 ³ /uL	150–450	reference	-	-
	<150	2.68	1.74–4.14	<0.001
	>450	1	0.55–1.82	1
WBC ×10 ³ /uL	>11	1.62	1.08–2.43	0.02
Neutrophil-to-lymphocyte ratio	≥4.7	2.5	1.79–3.50	<0.001
Albumin g/dL	<3.8	2.48	1.68–3.65	<0.001
Alkaline phosphatase IU/L	≥100	1.51	1.06–2.14	0.02

Fig. 2. This shows the Kaplan-Meier curve by strata of serum alkaline phosphatase over a one year period.

Table 4
Multivariate analysis of one-year mortality (n = 1090).

Variable	Category	OR	95% CI	p-value
One-year mortality				
Age years	≥65	1.62	1.20–2.20	0.002
BMI kg/m ²	18–30	reference	-	-
	<18	2.55	0.52–12.47	0.25
	>30	0.92	0.66–1.29	0.64
Primary tumor	Slow growth	reference	-	-
	Moderate growth	2.1	1.46–3.02	<0.001
	Rapid growth	8.43	5.68–12.53	<0.001
Lower extremity	-	1.41	0.99–1.99	0.05
Other bone metastases		1.95	1.35–2.80	<0.001
Visceral metastases		1.83	1.32–2.54	<0.001
Brain metastases		2.21	1.32–3.69	0.003
Hemoglobin g/dL	≤10	3.11	2.06–4.71	<0.001
Platelets x10 ³ /uL	150–450	reference	-	-
	<150	2.77	1.72–4.46	<0.001
	>450	0.81	0.41–1.62	0.56
Platelet-to-lymphocyte ratio	≥408	2.28	1.61–3.24	<0.001
Albumin g/dL	<3.8	1.67	1.21–2.31	0.002
Alkaline phosphatase IU/L	≥100	1.45	1.06–1.99	0.02

4.4. Prognostic algorithms for bone metastatic disease

Several prognostic factors have been identified in extremity metastatic bone disease and multiple prognostic models have been developed in order to aid survival estimation and surgical decision making.^{4–7} In the prognostic models that currently exist for extremity metastasis, hemoglobin is the most frequently used laboratory factor.^{5–7} Forsberg et al. also studied absolute lymphocyte count⁶ and Katagiri et al. studied clusters of laboratory factors which grouped as “abnormal” (CRP ≥ 0.4 mg/dL, LDH ≥ 250 IU/L, or serum albumin <3.7 g/dL) or “critical” (platelets <100,000/L, serum calcium ≥10.3 mg/dL, or total bilirubin ≥1.4 mg/dL).⁴ We previously developed machine learning algorithms in which multiple laboratory factors were included, among which alkaline phosphatase.⁷ The purpose of that study to explore the use of machine learning for the development of prognostic algorithms, and the variables were selected by random forest algorithms. In the current study we more thoroughly explored the use of alkaline phosphatase as a prognostic marker in extremity metastatic bone disease and our results suggest that the addition of serum alkaline phosphatase may improve prognostication in this population.

4.5. Limitations

There are several limitations to this study. First, this was a retrospective study and future prospective studies are needed to confirm the findings presented here. Additionally, only patients that were surgically managed were included and the prognostic value of serum alkaline phosphatase in patients managed non-operatively remains to be determined. Furthermore, the patient cohort from this study was drawn from two affiliated institutions from a single healthcare system. Future studies must determine whether the same results apply to a more heterogeneous population.

5. Conclusions

Elevated serum alkaline phosphatase is associated with greater bone metastatic tumor burden and with higher three-month and one-year mortality in patients with metastatic cancer affecting the extremities. Serum alkaline phosphatase should therefore be considered in prognostic models to estimate survival in this group of patients.

Funding

No external funding was sought for this study.

Ethical review committee statement

Our institutional review board approved of this study.

Location

This research was performed at the Massachusetts General Hospital in Boston, MA, United States of America.

Authors' contribution

Quirina C.B.S. Thio: Study conception and design - data collection - data analysis - drafting article - revision of article. Aditya V. Karhade: Study conception and design - data analysis - revision of article. Emily Notman: Data acquisition - revision of article. Kevin Raskin: Study design - data collection - revision of article. Santiago A. Lozano-Calderón: Study design - revision of article. Marco L. Ferrone: Interpretation of the data - revision of article. Jos A.M. Bramer: Interpretation of the data - revision of article. Joseph H. Schwab: Study conception and design - interpretation of the data - revision of the article.

All authors have reviewed and agreed to their individual contributions prior to submission.

Declaration of competing interest

None.

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