# Serum alkaline phosphatase and 30-day mortality after surgery for spinal metastatic disease

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CLINICAL STUDY

# Serum alkaline phosphatase and 30-day mortality after surgery for spinal metastatic disease

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## Abstract

**Background** Elevated serum alkaline phosphatase has been previously studied as a biomarker for progression of metastatic disease and implicated in adverse skeletal events and worsened survival. The purpose of this study was to determine if serum alkaline phosphatase was a predictor of short-term mortality of patients undergoing surgery for spinal metastatic disease.

**Methods** The American College of Surgeons National Surgical Quality Improvement Program was queried for patients undergoing spinal surgery for metastatic disease. Bivariate and multivariable analyses was undertaken to determine the relationship between serum alkaline phosphatase and 30-day mortality.

**Results** For the 1788 patients undergoing operative intervention for spinal metastatic disease between 2009 and 2016 the 30-day mortality was 8.49% (n = 151). In patients who survived beyond 30-days after surgery, n = 1627 (91.5%) the median [interquartile range] serum alkaline phosphatase levels were 126.4 [75–138], whereas in patients who had 30-day mortality, the serum alkaline phosphatase levels were 179.8 [114–187]. The optimal cut-off for alkaline phosphatase was determined to be 113 IU/L. On multivariable analysis, elevated serum alkaline phosphatase levels were associated with 30-day mortality (OR 1.61, 95% CI 1.12–2.32, p = 0.011).

**Conclusion** Elevated preoperative serum alkaline phosphatase is a marker for 30-day mortality in patients undergoing surgery for spinal metastatic disease. Future retrospective and prospective study designs should incorporate assessment of this serum biomarker to better understand the role for serum alkaline phosphatase in improving prognostication in spinal metastatic disease.

**Keywords** Alkaline phosphatase · Spine tumor · Metastases · 30-day · Survival

## Background

Bone metastatic disease inadvertently develops in 70% of breast and prostate cancer patients and spinal metastatic disease develops in 40% of all oncology patients [1, 2]. Patchell et al. previously demonstrated the benefit of decompressive surgery and radiotherapy versus radiotherapy alone for patients with spinal metastases [3]. However, in this subset of patients considered for surgery, pre-operative prognostic factors are critical for shared decision-making when considering short-term post-operative complications.

Alkaline phosphatase has been previously studied as biomarker for progression of bone metastatic disease [2]. In patients with small-cell lung cancer, elevated serum alkaline phosphatase has been associated with shorter survival [4]. In addition, elevated alkaline phosphatase has also been associated with spinal cord compression in a retrospective study of breast cancer patients from a phase III randomized controlled trial of zoledronic acid [5].

On the basis of these studies and the known biological mechanisms of bone metastatic disease, we hypothesized that elevated serum alkaline phosphatase would be a marker for poor short-term outcomes after surgery for spinal metastatic disease. In particular, we hypothesized that levels of serum alkaline phosphatase above the normal limit would be associated with increased 30-day mortality and morbidity.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s11060-018-2947-9) contains supplementary material, which is available to authorized users.

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## Methods

### Guidelines

This study followed the guidelines proposed by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [6], the Transparent Reporting of Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) [7], and the Reporting Recommendations for Tumor Marker Studies (REMARK) [8].

### Data source

The American College of Surgeons National Surgical Quality Improvement Program is a prospectively collected clinical registry of surgical centers in North America extensively studied in surgical and spinal outcomes research [9, 10]. Trained surgical reviewers collect pre-operative and 30-day postoperative data from randomly assigned patients at participating centers on an 8-day cycle. The database has been previously used to validate prognostic risk scores for postoperative survival in spinal metastatic disease [11–14].

### Participants

We queried the NSQIP database to identify patients that met the following criteria for inclusion (1) age 18 years or older (2) current procedural terminology (CPT) code for operative spinal intervention (corpectomy, laminectomy, fusion) at the cervical, thoracic or lumbosacral levels (3) confirmed International Classification of Disease diagnosis for secondary malignant neoplasm of bone, meninges, or spinal cord or pathologic fracture (4) comorbidity of disseminated cancer (5) American Society of Anesthesiologists classification indicating systemic disease (II-V) (6) general anesthesia (7) inpatient operation (8) subspecialty neurosurgery or orthopedics (9) year of operation 2009–2016 (Fig. 1).

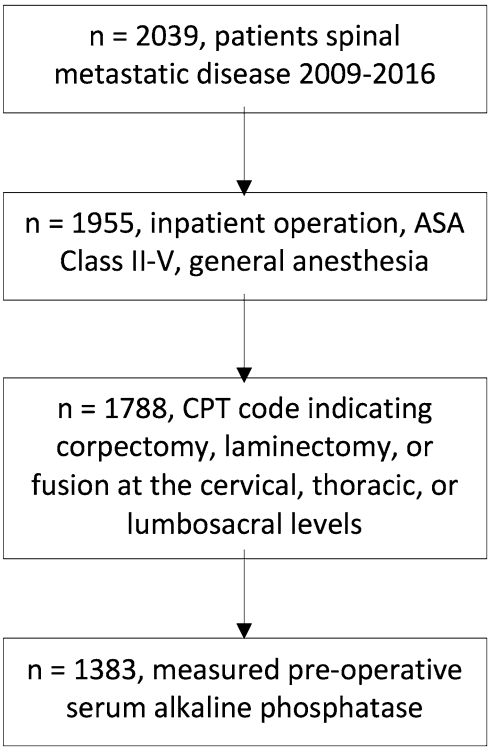


**Fig. 1** Study flowchart

### Outcomes

The primary dependent variable was 30-day mortality as defined in NSQIP as any intra-operative death or 30-day post-operative death from any-cause in any setting [inpatient or after discharge].

### Covariates

The following variables were extracted from NSQIP: age [younger than 65 years of age, 65 years of age or older], sex [male, female], body mass index [< 18.5, 18.5–25, 26–30, 30–35, > 35 ($kg/m^2$)], corpectomy [yes, no], laminectomy [yes, no], fusion [yes, no], instrumentation [yes, no], tumor location [cervical, thoracic, lumbosacral], preoperative functional status [independent, dependent], preoperative hematocrit [< 30, > 30 (%)], preoperative white blood cell count [< 11, ≥ 11 ($\times 10^3/\mu L$)], preoperative platelets [< 150, ≥ 150 ($\times 10^3/\mu L$)], preoperative albumin [< 3.5, > 3.5 (g/dL)], preoperative creatinine [< 1.4, > 1.4 (mg/dL)], bleeding disorder, American Society of Anesthesiologists Classification [II, III, IV–V], preoperative chronic corticosteroid or immunosuppressant medication use. Patients with dependent pre-operative functional status are defined in NSQIP as those requiring some or total assistance from others for activities of daily living before the index acute illness requiring surgical intervention. Bleeding disorder is defined in NSQIP as any hematologic disorder or continued administration of anticoagulant medication prior to surgery. Chronic steroid or immunosuppressant medication use is defined in NSQIP as requirement for regular oral or parenteral medication within 30-days prior to surgery excluding single pulses or short-courses < 10 days.

The optimal cutpoint method with the area under the receiver operating curve metric proposed by Lopez-Raton et al. was used to determine the threshold of 113 IU/L for serum alkaline phosphatase for the outcome of 30-day mortality [15]. Serum alkaline phosphatase was collected as part of routine liver function tests at a median of 3 days (interquartile range 1–8 days) before surgery.

## Missing data

Baseline rates of missing data were assessed for each variable and missing data was imputed with the non-parametric multiple imputation missForest method, based on the machine learning methodology of random forests [16].

## Statistical analysis

Descriptive statistics were generated for baseline characteristics of the study population and bivariate tests were conducted with univariable logistic regression for association with baseline characteristics and post-operative outcomes. Kaplan–Meier curves with 95% confidence intervals were generated for each strata of patients with normal and elevated serum alkaline phosphatase. Multivariable logistic regression for the postoperative outcomes of interest was conducted with 100-fold bootstrapped forward and backward stepwise elimination using the Akaike information criteria (AIC). All analyses were conducted with R version 3.4.4 and RStudio version 1.0.153.

## Results

Of the 1788 patients undergoing operative intervention for spinal metastatic disease, the 30-day mortality was 8.49% (n = 151). Overall, n = 773 (43.5%) of patients were 65 years of age or older and n = 688 (38.7%) were female (Table 1). In patients who survived beyond 30-days after surgery, n = 1627 (91.5%) the median [interquartile range] serum alkaline phosphatase levels were 126.4 [75–138], whereas in patients who suffered 30-day mortality, the serum alkaline phosphatase levels were 179.8 [114–187].

The optimal cut-off for alkaline phosphatase was determined to be 113 IU/L. The 30-day rate of mortality for patients with elevated serum alkaline phosphatase levels was 12.2% compared to 7.05% for patients with serum alkaline phosphatase levels below 113 IU/L (Fig. 2). On bivariate analysis, 30-day mortality was associated with male sex [OR 1.55, p = 0.018], dependent functional status [OR 2.74, p < 0.001], severity and extent of comorbid disease as defined by American Society of Anesthesiology Class IV–V [OR 5.24, p < 0.001], cervical tumor location relative to thoracic [OR 1.56, p = 0.030], bleeding disorder [OR 2.52, p < 0.001], anemia [OR 2.38, p < 0.001], leukocytosis [OR 1.41, p = 0.014], thrombocytopenia [OR 2.12, p < 0.001], hypoalbuminemia [OR 4.81, p < 0.001] (Table 2).

On bivariate analysis, elevated serum alkaline phosphatase levels (≥ 113 IU/L) were associated with 2.29 odds ratio [95% CI 1.64–3.21], p < 0.001 of 30-day mortality. On

**Table 1** Baseline characteristics of study population, n = 1788

| Variable | Definition | Total, n = 1788 |
|---|---|---|
| Sex | Female | 688 (38.7) |
| | Male | 1088 (61.3) |
| Age (years) | < 65 | 1005 (56.5) |
| | ≥ 65 | 773 (43.5) |
| Body mass index (kg/m$^2$) | 18.5–24.9 | 584 (32.8) |
| | < 18.5 | 140 (7.9) |
| | ≥ 35 | 166 (9.3) |
| | 25–29.9 | 582 (32.7) |
| | 30–34.9 | 306 (17.2) |
| Functional status | Independent | 1543 (86.8) |
| | Dependent | 229 (12.9) |
| | Unknown | 6 (0.3) |
| American Society of Anesthesiologist Class | II | 210 (11.8) |
| | III | 1150 (64.7) |
| | IV–V | 418 (23.5) |
| Laminectomy | No | 535 (30.1) |
| | Yes | 1243 (69.9) |
| Corpectomy | No | 1240 (69.7) |
| | Yes | 538 (30.3) |
| Fusion | No | 551 (31.0) |
| | Yes | 1227 (69.0) |
| Instrumentation | No | 678 (38.1) |
| | Yes | 1100 (61.9) |
| Tumor location | Thoracic | 1039 (58.4) |
| | Cervical | 325 (18.3) |
| | Lumbosacral | 414 (23.3) |
| Chronic steroid use | No | 1457 (81.9) |
| | Yes | 321 (18.1) |
| Bleeding disorder | No | 1653 (93.0) |
| | Yes | 125 (7.0) |
| Hematocrit (%) | ≥ 30 | 1249 (70.2) |
| | < 30 | 520 (29.2) |
| | Unknown | 9 (0.5) |
| White blood cell ($10^3$/μL) | 4–11 | 1261 (70.9) |
| | < 4 | 506 (28.5) |
| | Unknown | 11 (0.6) |
| Alkaline phosphatase (IU/L) | < 113 | 823 (46.3) |
| | ≥ 113 | 550 (30.9) |
| | Unknown | 405 (22.8) |
| Platelets ($10^3$/μL) | ≥ 150 | 1555 (87.5) |
| | < 150 | 215 (12.1) |
| | Unknown | 8 (0.4) |
| Albumin (g/dL) | ≥ 3.5 | 833 (46.9) |
| | < 3.5 | 543 (30.5) |
| | Unknown | 402 (22.6) |
| Creatinine (mg/dL) | < 1.4 | 1637 (92.1) |
| | ≥ 1.4 | 123 (6.9) |
| | Unknown | 18 (1.0) |

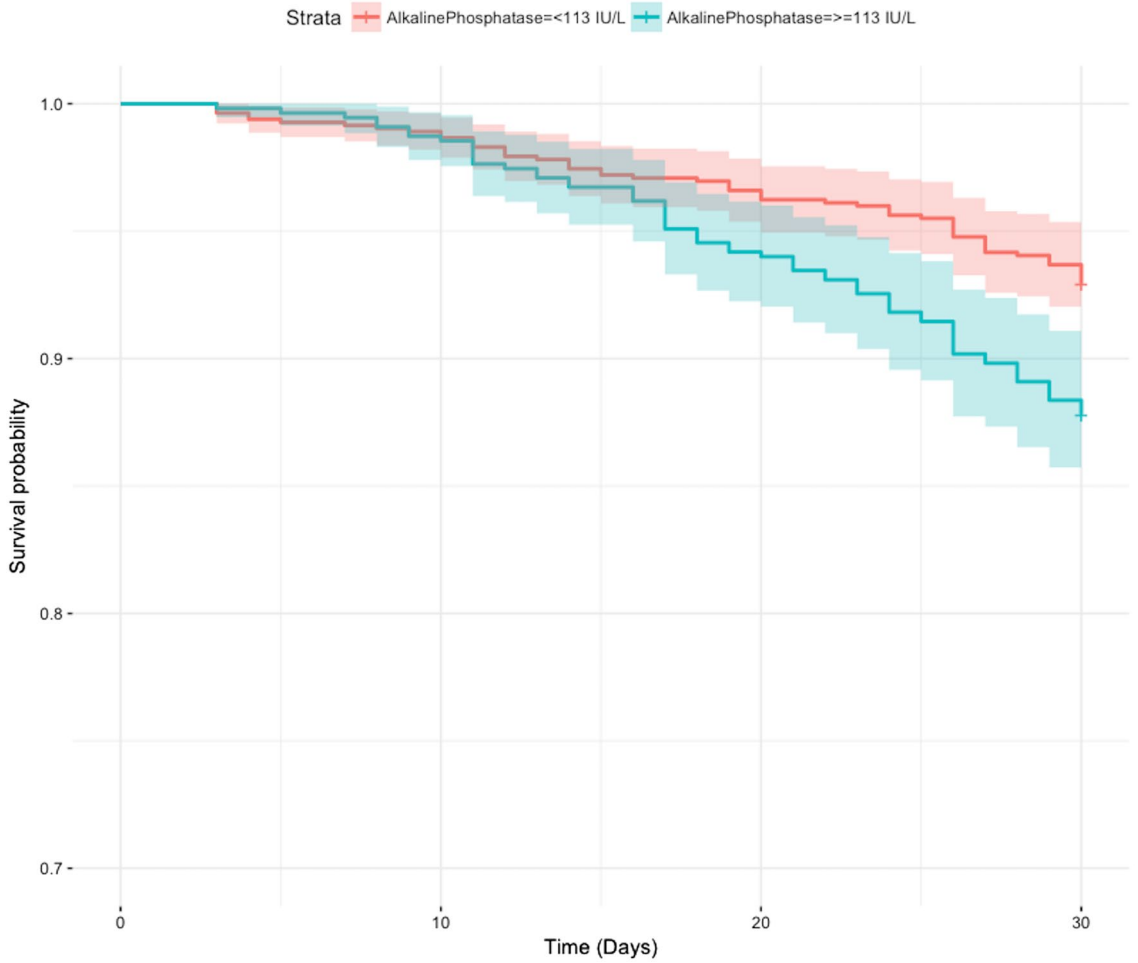


**Fig. 2** Kaplan–Meier curves with 95% confidence intervals by serum alkaline phosphatase strata

multivariable analysis, elevated serum alkaline phosphatase levels were associated with OR 1.61 [95% CI 1.12–2.32, p = 0.011] of 30-day mortality (Table 3).

## Discussion

In this study, elevated preoperative serum alkaline phosphatase was significantly associated with increased risk of 30-day mortality on bivariate analysis. Additionally, on multivariate analysis, controlling for sex, functional status, extent and severity of comorbid disease (American Society of Anesthesiologist Classification), instrumentation, bleeding disorder, tumor location, leukocytosis, thrombocytopenia, and hypoalbuminemia, elevated serum alkaline phosphatase remained significantly associated with increased risk of 30-day mortality.

Verlaan et al. previously conducted a prospective, multicenter international study of 1266 patients undergoing surgery for spinal metastatic disease and found older age and poor Karnofsky performance status as significant risk factors for < 3 month mortality [17]. The study assessed several important candidate prognostic factors for short-term survival in spinal metastatic disease but preoperative laboratory values were not assessed. Schoenfeld et al. studied 30- and 90-day survival after surgery for spinal metastases in 318 patients and determined that nutritional status and ambulatory capacity increased survival at 30-days. Primary cancer type was not associated with 30-day survival and lung cancer decreased survival at 90 days [18]. The association of elevated serum alkaline phosphatase in this study adds to the existing literature of short-term mortality after surgery for spinal metastatic disease.

Previous work in basic biology and clinical research has given some understanding of the role of alkaline phosphatase as a marker for progression of metastatic disease. For example, Achbarou et al. studied urokinase as a growth factor for osteoblast cells in prostate cancer; they transfected over-expressing urokinase into prostate carcinoma cells and inoculated these cancer cells into male Copenhagen rats and

**Table 2** Bivariate analysis of 30-day mortality with baseline characteristics, n = 1778

| Outcome | Definition | Odds ratio | 95% confidence interval | p-value |
|---|---|---|---|---|
| Sex | Female | Ref. | – | – |
| | Male | 1.55 | 1.08–2.24 | 0.018 |
| Age (years) | < 65 | Ref. | – | – |
| | ≥ 65 | 1.14 | 0.81–1.59 | 0.46 |
| Body mass index (kg/m$^2$) | 18.5–24.9 | Ref. | – | – |
| | < 18.5 | 1.51 | 0.82–2.66 | 0.16 |
| | ≥ 35 | 0.93 | 0.47–1.71 | 0.82 |
| | 25–29.9 | 1.09 | 0.73–1.65 | 0.67 |
| | 30–34.9 | 0.72 | 0.41–1.23 | 0.25 |
| Functional status | Independent | Ref. | – | – |
| | Dependent | 2.74 | 1.84–4.03 | < 0.001 |
| American Society of Anesthesiologist Class | II | Ref. | – | – |
| | III | 2.17 | 1.06–5.23 | 0.054 |
| | IV–V | 5.24 | 2.52–12.77 | < 0.001 |
| Laminectomy | No | Ref. | – | – |
| | Yes | 1.09 | 0.79–1.59 | 0.65 |
| Corpectomy | No | Ref. | – | – |
| | Yes | 0.85 | 0.58–1.22 | 0.39 |
| Fusion | No | Ref. | – | – |
| | Yes | 0.77 | 0.54–1.09 | 0.13 |
| Instrumentation | No | Ref. | – | – |
| | Yes | 0.73 | 0.52–1.03 | 0.069 |
| Tumor location | Thoracic | Ref. | – | – |
| | Cervical | 1.56 | 1.04–2.30 | 0.030 |
| | Lumbosacral | 0.71 | 0.44–1.11 | 0.15 |
| Chronic steroid use | No | Ref. | – | – |
| | Yes | 1.09 | 0.70–1.64 | 0.70 |
| Bleeding disorder | No | Ref. | – | – |
| | Yes | 2.52 | 1.51–4.07 | < 0.001 |
| Alkaline phosphatase (IU/L) | < 113 | Ref. | – | – |
| | ≥ 113 | 2.29 | 1.64–3.21 | < 0.001 |
| Hematocrit (%) | ≥ 30 | Ref. | – | – |
| | < 30 | 2.38 | 1.70–3.34 | < 0.001 |
| White blood cell ($10^3$/μL) | < 11 | Ref. | – | – |
| | ≥ 11 | 2.20 | 1.57–3.09 | < 0.001 |
| Platelets ($10^3$/μL) | ≥ 150 | Ref. | – | – |
| | < 150 | 2.12 | 1.38–3.19 | < 0.001 |
| Albumin (g/dL) | ≥ 3.5 | Ref. | – | – |
| | < 3.5 | 4.81 | 3.36–7.02 | < 0.001 |
| Creatinine (mg/dL) | < 1.4 | Ref. | – | – |
| | ≥ 1.4 | 1.30 | 0.68–2.29 | 0.39 |

found that these animals developed spinal cord compression and hind limb paralysis earlier than rats inoculated with under-expressing urokinase carcinoma cells. Notably, the over-expressing urokinase carcinoma group had more widespread skeletal metastases, higher serum alkaline phosphatase levels and increased osteoblastic activity on histological examination of lumbar metastases [19].

Clinical studies in prostate and breast cancer have found increased incidence of skeletal complications in patients with elevated alkaline phosphatase levels [5, 20]. In small cell lung cancer metastatic to the spine, higher serum alkaline phosphatase has been associated with worse overall survival [4]. Serum alkaline phosphatase can be a marker for progression of bone or liver disease and elevated serum

**Table 3** Multivariable logistic regression for 30-day mortality, n = 1778

| Variable | Definition | Odds ratio | 95% CI | P-value |
|---|---|---|---|---|
| Sex | Female | Ref. | – | – |
| | Male | 1.60 | 1.09–2.38 | 0.018 |
| Functional status | Independent | Ref. | – | – |
| | Dependent | 2.02 | 1.31–3.08 | 0.0012 |
| American Society of Anesthesiologist Class | II | Ref. | – | – |
| | III | 1.52 | 0.72–3.74 | 0.31 |
| | IV–V | 2.75 | 1.27–6.87 | 0.017 |
| Instrumentation | No | Ref. | – | – |
| | Yes | 0.74 | 0.51–1.08 | 0.12 |
| Bleeding disorder | No | Ref. | – | – |
| | Yes | 1.92 | 1.09–3.26 | 0.019 |
| Tumor location | Thoracic | Ref. | – | – |
| | Cervical | 1.75 | 1.13–2.68 | 0.011 |
| | Lumbosacral | 0.87 | 0.52–1.40 | 0.57 |
| Alkaline phosphatase (IU/L) | < 113 | Ref. | – | – |
| | ≥ 113 | 1.61 | 1.12–2.32 | 0.011 |
| White blood cell ($10^3$/μL) | < 11 | Ref. | – | – |
| | ≥ 11 | 2.18 | 1.51–3.16 | < 0.001 |
| Platelets ($10^3$/μL) | < 150 | Ref. | – | – |
| | ≥ 150 | 1.77 | 1.10–2.81 | 0.017 |
| Albumin (g/dL) | < 3.5 | Ref. | – | – |
| | ≥ 3.5 | 3.33 | 2.26–4.98 | < 0.001 |

alkaline phosphatase levels has shown to improve screening for liver metastasis with carcinoembryonic antigen (CEA) [21]. In a study of 3825 colorectal cancer patients treated with 5-fluorouracil, elevated serum alkaline phosphatase was associated with worse survival [22].

Though this the first study to our knowledge to examine the effect of alkaline phosphatase levels on short-term mortality after surgery for spinal metastatic disease, there are several limitations that must be addressed by future work. As gamma-glutamyl transferase or the presence or number of liver and skeletal metastases was not available in the NSQIP database, this study cannot differentiate between the elevated risk of short-term mortality in the setting of elevated serum alkaline phosphatase as a result of liver metastasis or bone metastasis. In addition, prognostic factors that others have found for long-term survival in spinal metastatic disease such as primary tumor histology could not be examined in this analysis; however, alkaline phosphatase remained significantly associated with 30-day mortality after controlling for other factors previously associated with 30-day mortality [17, 18]. Another limitation of the present study is the inability to study the effect of alkaline phosphatase on spinal metastatic disease patients who were managed non-operatively. Finally, although NSQIP is a clinical registry with many benefits of multi-institutional national data collection, the data completeness and data quality may be less than that of a single-institutional physician collected database or data collected prospectively for a specific study design.

As a result, there are many future studies that can be undertaken with the findings of this initial study of serum alkaline phosphatase as a biomarker for 30-day mortality in spinal metastatic disease. In particular, prospective studies should collect readily available serum blood tests (compete blood count, liver function tests) and further examine the role of serum biomarkers in helping determine prognosis for patients undergoing surgery for spinal metastatic disease.

## Conclusion

Elevated preoperative serum alkaline phosphatase is a marker for 30-day mortality in patients undergoing surgery for spinal metastatic disease. Future retrospective and prospective study designs should incorporate assessment of this serum biomarker to better understand the role for serum alkaline phosphatase in improving prognostication in spinal metastatic disease.

### Compliance with ethical standards

**Conflict of interest** No conflicts of interest to disclose.

**Ethical approval** The HIPPA-compliant de-identified NSQIP database has been exempted from individual review by our institutional review board.

## References


1. Barzilai O, Laufer I, Yamada Y et al (2017) Integrating evidence-based medicine for treatment of spinal metastases into a decision framework: neurologic, oncologic, mechanicals stability, and systemic disease. J Clin Oncol 35(21):2419–2427
2. Roodman GD (2004) Mechanisms of bone metastasis. N Engl J Med 350(16):1655–1664
3. Patchell RA, Tibbs PA, Regine WF et al (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 366(9486):643–648
4. Kang EJ, Lee SY, Kim HJ et al (2016) Prognostic factors and skeletal-related events in patients with small cell lung cancer with bone metastases at the time of diagnosis. Oncology 90(2):103–111
5. Brown JE, Cook RJ, Lipton A, Costa L, Coleman RE (2010) Prognostic factors for skeletal complications from metastatic bone disease in breast cancer. Breast Cancer Res Treat 123(3):767–779
6. Von Elm E, Altman DG, Egger M et al (2007) The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 4(10):e296
7. Collins GS, Reitsma JB, Altman DG, Moons KG (2015) Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMC Med 13(1):1
8. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM (2006) REporting recommendations for tumor MARKer prognostic studies (REMARK). Breast Cancer Res Treat 100(2):229–235
9. Raval MV, Pawlik TM (2018) Practical guide to surgical data sets: national surgical quality improvement program (NSQIP) and pediatric NSQIP. JAMA Surg. https://doi.org/10.1001/jamasurg.2018.0486
10. Karhade AV, Larsen AMG, Cote DJ, Dubois HM, Smith TR (2017) National databases for neurosurgical outcomes research: options, strengths, and limitations. Neurosurgery. https://doi.org/10.1093/neuros/nyx408
11. Hussain AK, Vig KS, Cheung ZB et al (2017) The impact of metastatic spinal tumor location on 30-day perioperative mortality and morbidity after surgical decompression. Spine (Phila Pa 1976) 43:E648–E655
12. Schoenfeld AJ, Le HV, Marjoua Y et al (2016) Assessing the utility of a clinical prediction score regarding 30-day morbidity and mortality following metastatic spinal surgery: the New England Spinal Metastasis Score (NESMS). Spine J 16(4):482–490
13. Sarkiss CA, Hersh EH, Ladner TR et al (2018) Risk factors for thirty-day morbidity and mortality in extradural lumbar spine tumor resection. World Neurosurg 114:e1101–e1106
14. Karhade AV, Vasudeva VS, Dasenbrock HH et al (2016) Thirty-day readmission and reoperation after surgery for spinal tumors: a National Surgical Quality Improvement Program analysis. Neurosurg Focus 41(2):E5
15. López-Ratón M, Cadarso-Suárez C, Gude-Sampedro F (2014) OptimalCutpoints: an R package for selecting optimal cutpoints in diagnostic tests. J Stat Softw 61:1–36
16. Stekhoven DJ, Bühlmann P (2011) MissForest—non-parametric missing value imputation for mixed-type data. Bioinformatics 28(1):112–118
17. Verlaan JJ, Choi D, Versteeg A et al (2016) Characteristics of patients who survived < 3 months or > 2 years after surgery for spinal metastases: can we avoid inappropriate patient selection? J Clin Oncol 34(25):3054–3061
18. Schoenfeld AJ, Leonard DA, Saadat E, Bono CM, Harris MB, Ferrone ML (2016) Predictors of 30- and 90-day survival following surgical intervention for spinal metastases: a prognostic study conducted at four academic centers. Spine (Phila Pa 1976) 41(8):E503–E509
19. Achbarou A, Kaiser S, Tremblay G et al (1994) Urokinase overproduction results in increased skeletal metastasis by prostate cancer cells in vivo. Cancer Res 54(9):2372–2377
20. Berruti A, Dogliotti L, Bitossi R et al (2000) Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline. J Urol 164(4):1248–1253
21. Tartter PI, Slater G, Gelernt I, Aufses AH Jr (1981) Screening for liver metastases from colorectal cancer with carcinoembryonic antigen and alkaline phosphatase. Ann Surg 193(3):357–360
22. Kohne CH, Cunningham D, Di Costanzo F et al (2002) Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol 13(2):308–317