Journal Pre-proof

The performance of frailty in predictive modeling of short-term outcomes in the surgical management of metastatic tumors to the spine

Joshua Bakhsheshian MD , Shane Shahrestani PhD ,
Zorica Buser PhD , Raymond Hah MD , Patrick C. Hsieh MD ,
John C. Liu MD , Jeffrey C. Wang MD

PII: S1529-9430(21)01049-4
DOI: <https://doi.org/10.1016/j.spinee.2021.11.015>
Reference: SPINEE 58598

To appear in: *The Spine Journal*

Received date: 28 June 2021
Revised date: 10 November 2021
Accepted date: 22 November 2021

Please cite this article as: Joshua Bakhsheshian MD , Shane Shahrestani PhD , Zorica Buser PhD , Raymond Hah MD , Patrick C. Hsieh MD , John C. Liu MD , Jeffrey C. Wang MD , The performance of frailty in predictive modeling of short-term outcomes in the surgical management of metastatic tumors to the spine, *The Spine Journal* (2021), doi: <https://doi.org/10.1016/j.spinee.2021.11.015>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc.

Clinical Study

**The performance of frailty in predictive modeling of short-term outcomes in
the surgical management of metastatic tumors to the spine**

Joshua Bakhsheshian MD^{1,*}, Shane Shahrestani PhD^{1,2,*}, Zorica Buser PhD^{1,3}, Raymond Hah
MD³, Patrick C. Hsieh MD¹, John C. Liu MD¹, Jeffrey C. Wang MD^{1,3}

¹Department of Neurological Surgery, Keck School of Medicine, University of Southern
California, Los Angeles, California, USA

²Department of Medical Engineering, California Institute of Technology, Pasadena, California,
USA

³Department of Orthopaedic Surgery, Keck School of Medicine, University of Southern
California, Los Angeles, California, USA

**These authors contributed equally.*

Corresponding author:

Zorica Buser, PhD

Department of Orthopaedic Surgery, Keck School of Medicine,
University of Southern California,
Los Angeles, California, USA.

Office: (323) 226-2271

Fax: (323) 226-7833

zbuser@usc.edu

Abstract**Background Context**

The concept of frailty has become increasingly recognized, and while patients with cancer are at increased risk for frailty, its influence on perioperative outcomes in metastatic spine tumors is uncertain.

Furthermore, the impact of frailty can be confounded by comorbidities or metastatic disease burden.

Purpose

The purpose of this study was to evaluate the influence of frailty and comorbidities on adverse outcomes in the surgical management of metastatic spine disease.

Study Design/Setting

Retrospective analysis of a nationwide database to include patients undergoing spinal fusion for metastatic spine disease.

Patient Sample

1,974 frail patients who received spinal fusion with spinal metastasis, and 1,975 propensity score matched non-frail patients.

Outcome Measures

Outcomes analyzed included mortality, complications, length of stay (LOS), nonroutine discharges and costs.

Methods

A validated binary frailty index (Johns Hopkins Adjusted Clinical Groups) was used to identify frail and non-frail groups, and propensity score-matched analysis (including demographics, comorbidities, surgical and tumor characteristics) was performed. Sub-group analysis of levels involved was performed for cervical, thoracic, lumbar and junctional spine. Multivariable-regression techniques were used to develop predictive models for outcomes using frailty and the Elixhauser Comorbidity Index (ECI).

Results

7,772 patients underwent spinal fusion with spinal metastasis, of which 1,974 (25.4%) patients were identified as frail. Following propensity score matching for frail (n= 1,974) and not-frail (n=1,975) groups, frailty demonstrated significantly greater medical complications (OR=1.58; 95% CI 1.33-1.86), surgical complications (OR=1.46; 95% CI 1.15-1.85), LOS (OR=2.65; 95% CI 2.09-3.37), nonroutine discharges (OR=1.79; 95% CI 1.46-2.20) and costs (OR=1.68; 95% CI 1.32-2.14). Differences in mortality were only observed in subgroup analysis and were greater in frail junctional and lumbar spine subgroups. Models using ECI alone (AUC= 0.636-0.788) demonstrated greater predictive ability compared to those using frailty alone (AUC=0.633-0.752). However, frailty combined with ECI improved the prediction of increased LOS (AUC=0.811), cost (AUC=0.768), medical complications (AUC=0.723) and nonroutine discharges (AUC=0.718). Predictive modeling of frailty in subgroups demonstrated the greatest performance for mortality (AUC=0.750) in the lumbar spine, otherwise performed similarly for LOS, costs, complications, and discharge across subgroups.

Conclusions

A high prevalence of frailty existed in the current patient cohort. Frailty contributed to worse short-term adverse outcomes and could be more influential in the lumbar and junctional spine due to higher risk of deconditioning in the postoperative period. Predictions for short term outcomes can be improved by adding frailty to comorbidity indices, suggesting a more comprehensive preoperative risk stratification should include frailty.

Keywords: cancer, physical function, prognosis, scoring system, machine learning

Introduction

Annually, more than 18,000 new metastatic spinal tumors are diagnosed in North America.[1] The vertebrae is the most common site of osseous metastases, commonly due to primary lung, breast, prostate, gastrointestinal tract, kidney, or thyroid neoplasms.[2–4] Despite major advancements in multi-disciplinary approaches, select candidates continue to benefit from additional surgical management.[5–8] However, surgical treatment in these patients is not without risk, with complication rates ranging from 10-

52% and mortality in up to 13%, which are commonly related to the severity of their medical or metastatic disease burden.[6,9–12]

As cancer survival rates continue to rise along with an aging population,[13] the surgical management of metastatic spinal tumors becomes more prevalent. Validated scoring systems are already available to aid surgical decision making for long-term survival.[5–8] However, preoperative risk assessment scores of short-term morbidity and mortality for undergoing spinal surgery is not straightforward, and is an important consideration in this vulnerable patient population. The Charlson Comorbidity Index (CCI) and the Elixhauser Comorbidity Index (ECI) are two common metrics that have been used to measure the burden of comorbidities while demonstrating a robust correlation with short and long-term outcomes.[14–16] Of the two, the ECI was shown to more effectively discriminate in-hospital outcomes for a variety of surgical cohorts, including patients undergoing spine surgery.[17–22] The predictive performance of ECI has not been established in surgical candidates with metastatic spine disease.

Recently, the concept of utilizing frailty as an independent risk factor in predicting short-term outcomes was popularized.[23–27] Frailty is described as cumulative age-related decline in physiological reserve and resiliency in response to stressors.[9,25,28] Patients with cancer are at increased risk for frailty, and this poses a formidable obstacle in their management. A number of studies have attempted to understand the predictive value of different frailty measures and comorbidity indices within the context of spine surgery, and despite significant advances, the precise role of specific frailty measurements and the degree of influence on surgical management of metastatic spinal tumors is unclear.[9,25,28–30] To address this gap in the literature, the authors aimed to investigate the influence of frailty on short-term outcomes in patients that underwent surgical management of their metastatic spinal tumor. Subsequently, the predictive influence of frailty was evaluated alongside a well-established comorbidity index (ECI).

Methods

Data Source

The Healthcare Cost and Utilization Project Nationwide Database was used from 2016-2017. This is a nationally representative inpatient database with information on patient demographics, diagnoses, procedures, and readmissions.[31] Institutional Review Board (IRB) approval was not required, since we used a de-identified publicly available database.

Patient Selection and Variables

Data regarding patient diagnoses and procedures was queried using International Classification of Diseases, 10 (ICD-10) codes. Patients receiving spinal fusion with spinal metastasis were included (**Figure 1**).[32] Patient frailty was queried using the Johns Hopkins Adjusted Clinical Groups (JHACG) frailty-defining diagnosis indicator, given its binary classification and validation for research using administrative data (**Supplemental Table 1**).[33–37] In contrast, the ECI uses 30 groups of diagnoses to measure the burden of their comorbidity (**Supplemental Table 1**).[17–20] The ECI was implemented using the R ‘comorbid’ package to obtain a comorbidity score for each patient.[14,38]

Propensity Score Matching

To quantify the influence of frailty within our patient population, nearest-neighbor propensity score matching for patient demographics, admission status (i.e. urgent/emergent), surgical approach, number of levels fused, spine location, ECI, discharge weights, and visceral metastases was implemented between frail and not-frail groups. The ‘MatchIt’ algorithm selects the best-fit parametric models based on the minimum ‘distance’ parameter, which is determined through logistic regression models that minimize the propensity score with no replacement.

Outcomes Analyzed

Outcomes included mortality, any medical complications, any surgical complications, neurological deterioration, length of stay (LOS, in top decile), all-payer hospital costs (top-decile), and nonroutine hospital discharges (**Supplemental Table 2**). Medical complications included postoperative infections, complications with intubation, acute kidney failure, pneumonia, myocardial infarction, cardiac arrest, thromboembolic events, pneumothorax, acute respiratory distress syndrome, and iatrogenic stroke.[9] Surgical complications included surgical-site infection, hematoma, wound complications, dysphagia,

incidental durotomy, mechanical implant-related complications, and paralytic ileus.[25] Nonroutine discharges were defined as discharges other than home.

Statistical Analysis

All statistics were conducted in RStudio (Version 1.2.5042) with $\alpha = 0.05$ level of significance. Odds ratios with post hoc chi-square testing were implemented using the 'Epitools' R package to compare rates of inpatient complications and hospital characteristics. Multivariable logistic regression models were developed and evaluated through receiver operating characteristic (ROC) curves. The area under the curve (AUC) of each ROC curve served as a proxy for model performance. In general, an AUC of 0.50 demonstrates a random guess and AUC values greater than 0.70 defined as acceptable.[39] There was no evidence of statistically poor fit based on Hosmer-Lemeshow testing. Because each arm of our analysis was independent from another, we utilized propensity score matching for direct comparisons of complications/outcomes and multivariable regression models with controlled covariates to generate predictive models and ROCs/AUCs. Missing data was omitted from statistical analysis.

Results

General Characteristics (All Patients)

7,772 patients underwent spinal fusion with spinal metastasis (**Figure 1**). Of these, the mean age was 62.3 (± 12.1) years and 41.8% listed as female. The majority of patients were non-elective admissions at metropolitan teaching hospitals. 1,974 (25.4%) patients were identified as frail, and the average ECI was 6.4 ± 3.2 . Additionally, 1,614 (20.8%) and 1,246 (16.0%) patients reported a history of radiation therapy and chemotherapy respectively. Further information on demographics, hospital and surgical characteristics were compiled in **Table 1**.

Propensity Score Matched Analysis of Outcomes

Following successful propensity score matching, the frail group included 1,974 patients and the not-frail group included 1,975 patients. No differences in demographics, ECI, myelopathy, vertebral body fracture, prior chemotherapy/radiation, surgical characteristics, presence of visceral metastases or primary tumor diagnoses were found between the two groups (**Table 1**). There was no difference in mortality between

the two groups. However, the frail group had higher rates of inpatient medical complications, surgical complications, LOS, nonroutine discharge and costs (**Table 3**).

Frailty vs Elixhauser Comorbidity Index

Three multivariable regression models were developed for each outcome, and were controlled for demographics and surgical characteristics. The first model used frailty alone, the second model used ECI, and the third used both frailty and ECI combined. Overall, models combining both frailty and ECI consistently performed better than those using either predictor alone (**Figure 2**), except for mortality (**Table 4, Table 5**). The ECI alone performed better at predicting mortality.

Frailty by Spinal Region

Patients were separated by whether they received fusion of the cervical, thoracic, lumbar, or crossing the junction of the spine following an operation for spinal metastasis (**Figure 1**). Multivariable regression analysis demonstrated that frailty was predictive of LOS, cost, complications, and nonroutine discharge in all subgroups (**Table 6**). However, frailty was predictive of mortality only when modeling lumbar and junctional fusion procedures. This finding was confirmed with ROC analysis, which demonstrated that frailty was most predictive of mortality (AUC=0.750) for lumbar spine subgroup; and LOS (AUC=0.762), complications (AUC=0.629), as well as nonroutine discharge (AUC=0.654) for cervical subgroup; and cost (AUC=0.714) for junctional subgroup (**Figure 3**). Models using frailty often had the lowest AUCs within the thoracic region, demonstrating frailty's inferior predictive value for metastasis to the thoracic spine (**Table 4, Table 5**).

Discussion

Surgical management of metastatic spine disease is complex, and can be associated with significant morbidity and mortality.[11,40–45] Approximately 25% of patients that underwent surgical management of their metastatic spine disease were identified as frail in the current study. This study showed that frailty, as defined by JHACG-FI, was independently associated with increased complications, LOS, non-routine discharges and costs. Therefore, incorporating JHACG-FI in clinical predictive models may

provide a more accurate depiction of the expected inpatient hospital course. With the advent of precision medicine using predictive analytics, the addition of the frailty metric can serve useful in future clinical decision support systems in spine surgery.[46,47] These factors can also be considered for health care quality and system improvements by evaluating the impact of earlier rehabilitation and nutritional optimization programs on improving outcomes in patients that are frail.

To date, a heterogeneous description of frailty parameters have been investigated in the assessment of patients undergoing spine surgery, of which only one evaluated patients with metastatic spinal tumors.[9,48] The concept of frailty is complex, as it can result from the interaction of clinical, functional, cognitive, psychological, and social factors, making it difficult to discern frailty related to disease, age-related frailty or unknown origins. It is important to discern the types of frailty, as they may require different interventions for management. Given that the extent of associated comorbidities and metastatic disease can contribute to frailty in our patient cohort, efforts were made to identify patients that were frail while controlling for associated comorbidities and tumor burden to minimize potential confounding. In contrast to prior observations,[25] a difference in short-term mortality was not observed between frail and not-frail groups. When patients included in the propensity-matched analysis were not controlled for associated comorbidities a significantly higher mortality rate was observed in the frail group.

De La Garza Ramos et al. reported a novel metastatic spinal tumor frailty index (MSTFI) based on a national database (2002-2011), and found it to predict mortality with an AUC of 0.644 and medical complications with an AUC of 0.671.[9] The MSTFI predictability performance for mortality decreased (AUC=0.565) when evaluating its external validity using an alternative large patient database. The MSTFI included 9 items that were associated risk factors for perioperative morbidity after surgery for metastatic spinal tumors. In contrast to the current study, the MSTFI incorporated comorbidities and variables outside of patient health or physiological factors, such as admission reason (i.e., emergent/urgent) and surgical approach (i.e., anterior, combined). The utility of the MSTFI was further questioned by a recent study by Massad et al, which failed to observe significant associations between MSTFI classes and outcomes.[49] Given that surgical invasiveness directly impacts outcomes, it has been

advocated that these features should be evaluated as a separate entity from frailty.[48] These factors were controlled for in the current study, and can explain the differences observed in mortality rates.

Despite differences in methodology, the current finding that frailty was associated with a higher-risk of developing medical complications is in line with prior reports.[9,48] These complications included wound dehiscence/infections, venous thromboembolism, pneumonia and others. These additional insults can result in a disproportionate change in health state in the frail group, i.e. lucid to delirious or independent to dependent states, resulting in greater LOS, nonroutine discharges, and overall costs. Even though admission status was included in the propensity match, it is possible that the prolonged LOS observed in the frail group was inflated, since the majority of patients, overall, were admitted urgently/emergently and were more prone to delays to surgery by obtaining additional medical clearance. The power of analyzing only elective admissions was too low for direct comparative analysis.

A wide range of methods in frailty assessment have been explored in spine surgery, likely due to the lack of a gold standard.[48,50] Frailty assessment in adult patients undergoing spinal surgery was observed to be a consistent predictor of mortality, morbidity, prolonged in-hospital LOS, and discharge to a center of higher care.[48] The most common FI reported in spine surgery is the modified FI (mFI), which is a scoring index that was developed on the theory of age- and disease-related deficit accumulation.[50] The mFI has proven to be a useful research tool in large administrative databases, but utilizes arbitrary cutoff values.[50] Its clinical utility remains unclear given the lack of standardized cutoff values that would delineate patients as frail or not-frail making it difficult to incorporate into preoperative planning. In contrast to other FIs, the JHACG-FI was formulated to capture multiple domains (i.e. functional, cognitive, psychological and socio-economic) of frailty, and has been shown to identify patients with limitations in activities of daily living.[33,36] It provides a comprehensive assessment of a patient's physical status with a binary result (frail or not-frail), and has been shown to predict long-term mortality in cardiovascular and other surgical procedures.[36,37] However, in contrast to continuous frailty metrics, the JHACG-FI may not capture differences amongst the degree of frailty. In addition, a previous systematic review by Veronesi et al. found that there may be an issue regarding the relationship between

the frailty level and gender, with worsening of frailty being prevalent in women, which represents an area of future research with regards to accuracy of frailty assessments.[51]

The FI is not intended to replace current validated scoring systems specific to prognostication of spinal metastatic disease,[8,12,52] rather the addition of FI evaluation may improve their predictability performance. Ghori et al. improved the predictability of survival from the modified Baur score[52] (AUC=0.64) by the addition of nutrition and ambulation (AUC=0.74), termed the New England Spinal Metastasis Score (NESMS).[11] Schoenfeld et al. validated the predictive ability for postoperative outcomes of patients from the National Surgical Quality Improvement Program (NSQIP; 2007–2013).[10] Despite their small sample size, they observed an AUC of 0.710 for mortality.[10] Including primary cancer type in the scoring system for prognostication of long term survival can become outdated as prognosis may change with advancements of adjuvant treatments.[5]

Predictive measures are only as good as the variables used to create it. To date, predictive modeling using combined frailty/comorbidity indices have not yet been evaluated within the context of metastatic spine disease. Due to the increased risk of comorbidities in the aging metastatic spine disease population, implementing a validated method for measuring comorbidities can increase the performance of prediction models. The ECI is a well-known risk adjustment model and has been shown to outperform the Charlson Comorbidity Index in predicting in-hospital outcomes.[22] In the current report, ECI demonstrated acceptable accuracy in predicting in-hospital mortality, complications, LOS and cost and the addition of JHACG-FI to ECI improved the predictive model, in all outcomes except mortality. The improvement in prediction performance was likely observed given that JHACG-FI captured domains of frailty that did not overlap with comorbidities measured by ECI, as the JHACG-FI was observed to be an independent predictor of outcomes when controlled for ECI.

Relative to the rigid thoracic spine the mobile lumbar spine entails a number of unique biomechanical and adjacent anatomical features, which can be associated with increased instability and complications that may independently impact surgical outcomes.[53,54] These factors include the transition of a rigid kyphotic thoracic spine (supported by the rib cage) to a more mobile lordotic lumbar spine with increased

weight bearing load of the vertebral bodies. To better characterize the predictive utility of frailty, we performed a subgroup analysis for each outcome by the spinal region involved and found that frailty most accurately predicted mortality in the lumbar spine. The finding likely stems from the FI capturing components of disabilities secondary to lesions in the thoracolumbar/lumbar spine, such as weaker trunk muscles with difficulties in ambulation and increased falls, therefore becoming higher risk for further deconditioning if bedbound in the immediate postoperative period. These observations were limited by a lower power in the subgroup analysis, as these differences were not observed in the matched comparative analysis in all spine groups.

Recent studies capturing frailty in the skeletal muscle (sarcopenia) domain through an objective measurement of psoas muscle size has been shown to predict overall survival.[47] Currently, the definition of sarcopenia also suffers the wide interpretation of components leading to its diagnoses, and the evaluation of psoas size is not always available. As such, by combining multiple domains reflective of a patient's overall health status, the JHACG-FI still allows for a simple test to identify frailty with stronger predictive performance in short-term outcomes than prior observations. Management of these patients is exceedingly complex and requires collaboration between multidisciplinary teams. The validation of assessment scores is important for preoperative risk stratification and improving outcomes in high-risk patient cohorts, as these patients may benefit from nutritional or rehabilitation interventions.[55] This study is not without limitations. First, by using a national database we were limited by the available data, in addition to limitations secondary to ICD coding. The dataset was missing granular information on laboratory parameters, surgical indications, tumor grade, extent of resection. Power analysis precluded additional stratification by tumor type. Propensity score matching and multivariable analysis was performed with the attempt to minimize confounding between our cohorts. The study was limited to consider only short-term perioperative events, given the major aim was to focus on this limited perioperative window. The inclusion of only spinal fusion candidates limits the external validity to candidates undergoing separation or decompression surgery only. Further, more than 40% of the matched cohort had unspecified primary tumor sites. However, this is mainly a limitation of the NRD and the

narrow scope of ICD-10 coding. Lastly, there was a risk of Berkson's bias and selection bias because of our use of an inpatient hospital database, which we aimed to minimize by using random methods when selecting subgroups, including large sample sizes, and matching for demographics, comorbidities, surgical characteristics, and extent of metastatic disease. Future prospective studies that account for variables unable to be captured in this study are needed. Despite the limitations above, obtaining a large sample size from multiple institutions for the purposes of evaluating a predictive model provides additional useful information to support additional higher-level investigations.

Conclusion

A large proportion of patients undergoing surgical management of their metastatic spine disease were frail. Frailty increased the risks for short-term adverse outcomes, independently from demographics, comorbidities, surgical, and tumor characteristics. Frailty could be more influential in the lumbar and junctional spine due to pre-existing ambulation deficits associated with higher risk for deconditioning in the postoperative period. Together, these findings suggest that the early postoperative period is a window of increased risk for patients that are frail, and they may benefit from earlier nutritional or rehabilitation programs. Therefore, including frailty metrics to identify patients with limitations in their activities of daily living should be implemented in the preoperative planning process. Furthermore, the performance of prediction models can be improved by adding frailty to established comorbidity indices.

Declaration of Competing Interest

No conflicts of interest for the current study. Disclosures outside of submitted work have been submitted within The Spine Journal Conflict of Interest forms.

Funding

JB funded by NIH NINDS R25NS099008 USC Neurosurgery Research Education Training Program. No funding for the current study

References

- [1] Raj VS, Lofton L. Rehabilitation and treatment of spinal cord tumors. *J Spinal Cord Med* 2013;36:4–11.
- [2] Ciftdemir M, Kaya M, Selcuk E, Yalniz E. Tumors of the spine. *World J Orthop* 2016;7:109–16.
- [3] Choi D, Crockard A, Bunger C, Harms J, Kawahara N, Mazel C, et al. Review of metastatic spine tumour classification and indications for surgery: the consensus statement of the Global Spine Tumour Study Group. *Eur Spine J* 2010;19:215–22.
- [4] Ziu E, Viswanathan VK, Mesfin FB. *Spinal Metastasis*. StatPearls, Treasure Island (FL): StatPearls Publishing; 2020.
- [5] Choi D, Bilsky M, Fehlings M, Fisher C, Gokaslan Z. Spine Oncology—Metastatic Spine Tumors. *Neurosurgery* 2017;80:S131–7.
- [6] Bilsky MH, Lis E, Raizer J, Lee H, Boland P. The diagnosis and treatment of metastatic spinal tumor. *Oncologist* 1999;4:459–69.
- [7] Bauer H, Tomita K, Kawahara N, Abdel-Wanis ME, Murakami H. Surgical strategy for spinal metastases. *Spine* 2002;27:1124–6.
- [8] Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine* 2005;30:2186–91.
- [9] De la Garza Ramos R, Goodwin CR, Jain A, Abu-Bonsrah N, Fisher CG, Bettgowda C, et al. Development of a Metastatic Spinal Tumor Frailty Index (MSTFI) Using a Nationwide Database and Its Association with Inpatient Morbidity, Mortality, and Length of Stay After Spine Surgery. *World Neurosurg* 2016;95:548–55.e4.
- [10] Schoenfeld AJ, Le HV, Marjoua Y, Leonard DA, Belmont PJ Jr, Bono CM, et al. 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* 2016;16:482–90.
- [11] Ghorri AK, Leonard DA, Schoenfeld AJ, Saadat E, Scott N, Ferrone ML, et al. Modeling 1-year survival after surgery on the metastatic spine. *Spine J* 2015;15:2345–50.
- [12] Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. *Spine* 2001;26:298–306.
- [13] Jacobs WB, Perrin RG. Evaluation and treatment of spinal metastases: an overview. *Neurosurg Focus* 2001;11:e10.
- [14] Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
- [15] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- [16] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
- [17] Chang H-J, Chen P-C, Yang C-C, Su Y-C, Lee C-C. Comparison of Elixhauser and Charlson Methods for Predicting Oral Cancer Survival. *Medicine* 2016;95:e2861.
- [18] Quail JM, Lix LM, Osman BA, Teare GF. Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. *BMC Health Serv Res* 2011;11:146.
- [19] Menendez ME, Neuhaus V, van Dijk CN, Ring D. The Elixhauser comorbidity method outperforms the Charlson index in predicting inpatient death after orthopaedic surgery. *Clin Orthop Relat Res* 2014;472:2878–86.
- [20] Liefers JR, Baracos VE, Winget M, Fassbender K. A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. *Cancer* 2011;117:1957–65.
- [21] Menendez ME, Ring D, Harris MB, Cha TD. Predicting In-Hospital Mortality in Elderly Patients With Cervical Spine Fractures: A Comparison of the Charlson and Elixhauser Comorbidity Measures. *Spine* 2015;40:809–15.

- [22] Maron SZ, Neifert SN, Ranson WA, Nystal DA, Rothrock RJ, Cooke P, et al. Elixhauser Comorbidity Measure is Superior to Charlson Comorbidity Index In-Predicting Hospital Complications Following Elective Posterior Cervical Decompression and Fusion. *World Neurosurg* 2020;138:e26–34.
- [23] Baldasseroni S, Pratesi A, Orso F, Forte AL, Baroncini AC, Lucarelli G, et al. Role of Frailty on Risk Stratification in Cardiac Surgery and Procedures. *Adv Exp Med Biol* 2020;1216:99–113.
- [24] Ko FC. Preoperative Frailty Evaluation: A Promising Risk-stratification Tool in Older Adults Undergoing General Surgery. *Clin Ther* 2019;41:387–99.
- [25] Miller EK, Neuman BJ, Jain A, Daniels AH, Ailon T, Sciubba DM, et al. An assessment of frailty as a tool for risk stratification in adult spinal deformity surgery. *Neurosurg Focus* 2017;43:E3.
- [26] Youngerman BE, Neugut AI, Yang J, Hershman DL, Wright JD, Bruce JN. The modified frailty index and 30-day adverse events in oncologic neurosurgery. *J Neurooncol* 2018;136:197–206.
- [27] Wilson JRF, Badhiwala JH, Moghaddamjou A, Yee A, Wilson JR, Fehlings MG. Frailty Is a Better Predictor than Age of Mortality and Perioperative Complications after Surgery for Degenerative Cervical Myelopathy: An Analysis of 41,369 Patients from the NSQIP Database 2010-2018. *J Clin Med Res* 2020;9. <https://doi.org/10.3390/jcm9113491>.
- [28] Yagi M, Michikawa T, Hosogane N, Fujita N, Okada E, Suzuki S, et al. The 5-Item Modified Frailty Index Is Predictive of Severe Adverse Events in Patients Undergoing Surgery for Adult Spinal Deformity. *Spine* 2019;44:E1083.
- [29] Flexman AM, Charest-Morin R, Stobart L, Street J, Ryerson CJ. Frailty and postoperative outcomes in patients undergoing surgery for degenerative spine disease. *Spine J* 2016;16:1315–23.
- [30] Lakomkin N, Zuckerman SL, Stannard B, Montejo J, Sussman ES, Virojanapa J, et al. Preoperative Risk Stratification in Spine Tumor Surgery: A Comparison of the Modified Charlson Index, Frailty Index, and ASA Score. *Spine* 2019;44:E782–7.
- [31] Healthcare Cost and Utilization Project (HCUP). Nationwide Readmissions Database 2016-2017.
- [32] Dasenbrock HH, Wolinsky J-P, Sciubba DM, Witham TF, Gokaslan ZL, Bydon A. The impact of insurance status on outcomes after surgery for spinal metastases. *Cancer* 2012;118:4833–41.
- [33] The Johns Hopkins Adjusted Clinical Groups Technical Reference Guide, version 9.0. Johns Hopkins University, Baltimore, MD; 2009.
- [34] Sternberg SA, Bentur N, Abrams C, Spalter T, Karpati T, Lemberger J, et al. Identifying frail older people using predictive modeling. *Am J Manag Care* 2012;18:e392–7.
- [35] Lieberman R, Abrams C, Weiner J. Development and evaluation of the Johns Hopkins University risk adjustment models for Medicare+ Choice plan payment. MD Baltimore 2003.
- [36] Tran DTT, Tu JV, Dupuis J-Y, Bader Eddeen A, Sun LY. Association of frailty and long-term survival in patients undergoing coronary artery bypass grafting. *J Am Heart Assoc* 2018;7. <https://doi.org/10.1161/JAHA.118.009882>.
- [37] McIsaac DI, Bryson GL, van Walraven C. Association of Frailty and 1-Year Postoperative Mortality Following Major Elective Noncardiac Surgery: A Population-Based Cohort Study. *JAMA Surg* 2016;151:538–45.
- [38] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.
- [39] Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. John Wiley & Sons; 2013.
- [40] Petteys RJ, Spitz SM, Rhee J, Goodwin CR, Zadnik PL, Sarabia-Estrada R, et al. Tokuhashi score is predictive of survival in a cohort of patients undergoing surgery for renal cell carcinoma spinal metastases. *Eur Spine J* 2015;24:2142–9.
- [41] Shehadi JA, Sciubba DM, Suk I, Suki D, Maldaun MVC, McCutcheon IE, et al. Surgical treatment strategies and outcome in patients with breast cancer metastatic to the spine: a review of 87 patients. *Eur Spine J* 2007;16:1179–92.
- [42] Zadnik PL, Hwang L, Ju DG, Groves ML, Sui J, Yurter A, et al. Prolonged survival following aggressive treatment for metastatic breast cancer in the spine. *Clin Exp Metastasis* 2014;31:47–55.

- [43] Sellin JN, Suki D, Harsh V, Elder BD, Fahim DK, McCutcheon IE, et al. Factors affecting survival in 43 consecutive patients after surgery for spinal metastases from thyroid carcinoma. *J Neurosurg Spine* 2015;23:419–28.
- [44] Ju DG, Zadnik PL, Groves ML, Hwang L, Kaloostian PE, Wolinsky J-P, et al. Factors associated with improved outcomes following decompressive surgery for prostate cancer metastatic to the spine. *Neurosurgery* 2013;73:657–66; discussion 666.
- [45] Goodwin CR, Khattab MH, Sankey EW, Elder BD, Kosztowski TA, Sarabia-Estrada R, et al. Factors Associated with Life Expectancy in Patients with Metastatic Spine Disease from Adenocarcinoma of the Lung. *Global Spine J* 2015;5:417–24.
- [46] Buchlak QD, Esmaili N, Leveque J-C, Farrokhi F, Bennett C, Piccardi M, et al. Machine learning applications to clinical decision support in neurosurgery: an artificial intelligence augmented systematic review. *Neurosurg Rev* 2020;43:1235–53.
- [47] Zakaria HM, Wilkinson BM, Pennington Z, Saadeh YS, Lau D, Chandra A, et al. Sarcopenia as a Prognostic Factor for 90-Day and Overall Mortality in Patients Undergoing Spine Surgery for Metastatic Tumors: A Multicenter Retrospective Cohort Study. *Neurosurgery* 2020;87:1025–36.
- [48] Moskven E, Bourassa-Moreau É, Charest-Morin R, Flexman A, Street J. The impact of frailty and sarcopenia on postoperative outcomes in adult spine surgery. A systematic review of the literature. *Spine J* 2018;18:2354–69.
- [49] Massaad E, Williams N, Hadzipasic M, Patel SS, Fourman MS, Kiapour A, et al. Performance assessment of the metastatic spinal tumor frailty index using machine learning algorithms: limitations and future directions. *Neurosurg Focus* 2021;50:E5.
- [50] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
- [51] Veronesi F, Borsari V, Martini L, Visani A, Gasbarrini A, Brodano GB, et al. The Impact of Frailty on Spine Surgery: Systematic Review on 10 years Clinical Studies. *Aging Dis* 2021;12:625–45.
- [52] Leithner A, Radl R, Gruber G, Hochegger M, Leithner K, Welkerling H, et al. Predictive value of seven preoperative prognostic scoring systems for spinal metastases. *Eur Spine J* 2008;17:1488–95.
- [53] Holman PJ, Suki D, McCutcheon I, Wolinsky J-P, Rhines LD, Gokaslan ZL. Surgical management of metastatic disease of the lumbar spine: experience with 139 patients. *J Neurosurg Spine* 2005;2:550–63.
- [54] Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine* 2010;35:E1221–9.
- [55] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;381:752–62.

Figure 1. Patient selection and analysis flowchart

Figure 2. ROC curves comparing the predictive abilities of frailty, Elixhauser scores, and frailty+Elixhauser scores. Top: ROC curves for top decile of LOS. Bottom: ROC curves for top decile of cost

Figure 3. ROC curves comparing the predictive capability of frailty by spinal region. Top: ROC curves mortality. Middle: ROC curves for top decile of LOS. Bottom: ROC curves for top decile of cost.

Table 1. Patient, surgical, tumor, and hospital characteristics for all patients receiving surgical intervention for a metastatic spinal tumor.

	All Patients (n=7,772)	Propensity Matched		
		Frail (n=1,974)	Not-Frail (n=1,975)	p-values
Age (years)	62.3±12.1	64.5±11.9	64.8±11.0	0.72
Sex (M:F)	1.392:1	1.625:1	1.876:1	0.79
Elixhauser Comorbidity	6.4±3.2	8.2±3.3	7.9±3.1	0.13
Insurance				
Medicare	3,573 (46.0%)	1,057 (53.5%)	1,057 (53.5%)	0.50
Medicaid	972 (12.5%)	240 (12.2%)	231 (11.7%)	
Private/Self-Pay	2,920 (37.6%)	603 (30.5%)	614 (31.1%)	
Hospital type				
Metropolitan non-teaching	841 (10.8%)	211 (10.7%)	238 (12.1%)	0.31
Metropolitan teaching	6,810 (87.6%)	1,720 (87.1%)	1,708 (86.5%)	
Number of Levels Fused				
Single-Level	1,671 (21.5%)	418 (21.2%)	406 (20.6%)	0.96
Multi-Level	6,101 (78.5%)	1,556 (78.8%)	1,569 (79.4%)	
Surgical Approach				
Anterior	847 (10.9%)	485 (24.5%)	504 (25.6%)	0.84
Posterior	5,825 (74.9%)	1,253 (63.5%)	1,237 (62.6%)	
Combined	1,100 (14.2%)	236 (12.0%)	234 (11.8%)	
Myelopathy	492 (6.3%)	183 (9.3%)	130 (6.6%)	0.080
Pathological VB Fracture	3,493 (44.9%)	925 (46.9%)	951 (48.2%)	0.80
Visceral Metastases	1,534 (19.7%)	695 (35.2%)	696 (35.2%)	0.93
Primary Tumor Site				
Lung	947 (12.2%)	266 (13.5%)	289 (14.6%)	0.92
Breast	908 (11.7%)	145 (7.3%)	152 (7.7%)	
Prostate	1,199 (15.4%)	316 (16.0%)	324 (16.4%)	
Kidney	687 (8.8%)	125 (6.3%)	178 (9.0%)	

Thyroid	216 (2.8%)	28 (1.4%)	45 (2.3%)	
Sarcoma	88 (1.1%)	28 (1.4%)	16 (0.8%)	
Lymphoma/Myeloma	241 (3.1%)	50 (2.5%)	46 (2.3%)	
Melanoma	202 (2.6%)	54 (2.7%)	26 (1.3%)	
Gastrointestinal/Digestive Organs	334 (4.3%)	116 (5.9%)	65 (3.3%)	
Unspecified	2,950 (38.0%)	846 (42.9%)	834 (42.2%)	
History of Radiation	1,614 (20.8%)	377 (19.1%)	338 (17.1%)	0.37
History of Chemotherapy	1,246 (16.0%)	300 (15.2%)	269 (13.6%)	0.42

Table 2. Postoperative outcomes for all patients. Comparisons are being made using chi-square tests between frail and non-frail patients.

	All Patients (n=7,772)	Propensity Matched		
		Frail Patients (n=1,974)	Non-Frail Patients (n=1,975)	p-values
Discharge location				
Routine/Home	2,495 (32.1%)	350 (17.9%)	548 (27.7%)	<0.0001*
Non-Routine	5,277 (67.9%)	1,621 (82.1%)	1,427 (72.3%)	
Neurological Complications	145 (1.9%)	75 (3.8%)	50 (2.5%)	0.28
Surgical Complications	915 (11.8%)	360 (18.2%)	246 (12.5%)	0.0016*
Mean All-Payer Cost	\$66,544.41±\$45,434.46	\$84,242.98±\$57,810.91	\$77,587.48±\$52,011.47	<0.0001*
Mean LOS (days)	12.9±11.6	19.9±15.0	13.6±10.5	<0.0001*

Table 3. Summary differences between propensity score matched frail and non-frail groups

Outcome	Frail Patients (n=1,974)	Propensity Matched Non-Frail Patients (n=1,975)	Odds Ratio	95% Confidence Interval	p-value
Mortality	107 (5.4%)	94 (4.8%)	1.28	0.88-1.86	0.19
Medical Complications	1,227 (62.2%)	998 (50.5%)	1.58	1.33-1.86	<0.0001*
Surgical Complications	360 (18.2%)	246 (12.5%)	1.46	1.15-1.85	0.0016*
LOS	465 (23.6%)	199 (10.1%)	2.65	2.09-3.37	<0.0001*
Nonroutine Discharge	1,621 (82.1%)	1,427 (72.3%)	1.79	1.46-2.20	<0.0001*

Cost	330 (16.7%)	206 (10.4%)	1.68	1.32-2.14	<0.0001*
------	-------------	-------------	------	-----------	----------

Table 4. Area under the curve (AUC) values for all ROC curves

<u>Frailty and ECI</u>	Mortality	Medical Complications	Surgical Complications	LOS	Nonroutine Discharge	Cost
Frailty	0.684	0.675	0.633	0.752	0.705	0.712
ECI	0.788	0.718	0.636	0.783	0.710	0.757
Frailty & ECI	0.788	0.723	0.650	0.811	0.718	0.768
<u>Frailty by subgroup</u>	Mortality	Medical Complications	Surgical Complications	LOS	Nonroutine Discharge	Cost
Cervical	0.613	0.629	0.620	0.762	0.654	0.648
Thoracic	0.573	0.624	0.575	0.691	0.599	0.689
Lumbar	0.750	0.621	0.651	0.687	0.600	0.692
Crossing Junctions	0.658	0.627	0.638	0.697	0.633	0.714

Table 5. P-values comparing all ROC curve AUC values.

<u>LOS</u>	Frailty	ECI	Frailty & ECI	NA
Frailty	NA	0.01*	<0.0001*	NA
ECI	NA	NA	<0.0001*	NA
Frailty & ECI	NA	NA	NA	NA
<u>LOS</u>	Cervical	Thoracic	Lumbar	Crossing Junctions
Cervical	NA	0.30	0.32	0.13
Thoracic	NA	NA	0.94	0.48
Lumbar	NA	NA	NA	0.58
Crossing Junctions	NA	NA	NA	NA
<u>Cost</u>	Frailty	ECI	Frailty & ECI	NA
Frailty	NA	<0.0001*	<0.0001*	NA
ECI	NA	NA	0.008*	NA
Frailty & ECI	NA	NA	NA	NA

<u>Cost</u>	Cervical	Thoracic	Lumbar	Crossing Junctions
Cervical	NA	0.04*	0.07	0.10
Thoracic	NA	NA	0.93	0.88
Lumbar	NA	NA	NA	0.83
Crossing Junctions	NA	NA	NA	NA
<u>Medical Complications</u>	Frailty	ECI	Frailty & ECI	NA
Frailty	NA	<0.0001*	<0.0001*	NA
ECI	NA	NA	0.008*	NA
Frailty & ECI	NA	NA	NA	NA
<u>Mortality</u>	Cervical	Thoracic	Lumbar	Crossing Junctions
Cervical	NA	0.54	0.03*	0.50
Thoracic	NA	NA	0.006*	0.21
Lumbar	NA	NA	NA	0.16
Crossing Junctions	NA	NA	NA	NA

Table 6. Multivariable analysis of frailty by spinal level. Demographics and surgical approaches were controlled for as covariates within each model.

Cervical	Frail Patients (n=401)	Non-Frail Patients (n=1,263)	Odds Ratio	95% Confidence Interval	p-value
Mortality	22 (5.5%)	43 (3.4%)	1.71	0.83-3.38	0.13
Medical Complications	209 (52.1%)	382 (30.2%)	2.55	1.86-3.48	<0.0001*
Surgical Complications	104 (25.9%)	190 (15.0%)	2.02	1.38-2.92	0.00023*
LOS	97 (24.2%)	59 (4.7%)	7.54	4.79-12.08	<0.0001*
Nonroutine Discharge	319 (79.6%)	646 (51.1%)	3.86	2.69-5.65	<0.0001*
Cost	60 (15.0%)	76 (6.0%)	3.18	2.03-4.97	<0.0001*
Thoracic	Frail Patients (n=747)	Non-Frail Patients (n=2,141)	Odds Ratio	95% Confidence	p-value

				Interval	
Mortality	29 (3.9%)	53 (2.5%)	1.64	0.87-2.98	0.11
Medical Complications	485 (64.9%)	955 (44.6%)	2.45	1.94-3.10	<0.0001*
Surgical Complications	95 (12.7%)	161 (7.5%)	1.67	1.16-2.39	0.0055*
LOS	173 (23.2%)	127 (5.9%)	4.48	3.22-6.24	<0.0001*
Nonroutine Discharge	634 (84.9%)	1,464 (68.4%)	2.47	1.85-3.36	<0.0001*
Cost	120 (16.1%)	100 (4.7%)	2.91	2.07-4.09	<0.0001*
Lumbar	Frail Patients (n=393)	Non-Frail Patients (n=1,278)	Odds Ratio	95% Confidence Interval	p-value
Mortality	20 (5.1%)	22 (1.7%)	2.98	1.39-6.35	0.0045*
Medical Complications	256 (65.1%)	540 (42.3%)	2.71	1.99-3.71	<0.0001*
Surgical Complications	72 (18.3%)	97 (7.6%)	2.63	1.71-4.02	<0.0001*
LOS	102 (26.0%)	70 (5.5%)	4.62	3.02-7.09	<0.0001*
Nonroutine Discharge	301 (76.6%)	784 (61.3%)	2.13	1.51-3.07	<0.0001*
Cost	53 (13.5%)	67 (5.2%)	2.49	1.58-3.90	<0.0001*
Crossing Junctions	Frail Patients (n=433)	Non-Frail Patients (n=1,115)	Odds Ratio	95% Confidence Interval	p-value
Mortality	36 (8.3%)	33 (3.0%)	3.47	1.84-6.64	0.00013*
Medical Complications	278 (64.2%)	466 (41.8%)	2.46	1.81-3.35	<0.0001*
Surgical Complications	89 (20.6%)	108 (9.7%)	2.06	1.33-3.16	0.0010*
LOS	94 (21.7%)	63 (5.7%)	4.06	2.61-6.35	<0.0001*
Nonroutine Discharge	366 (84.5%)	763 (68.4%)	2.64	1.79-3.98	<0.0001*
Cost	98 (22.6%)	113 (10.1%)	2.35	1.48-3.72	0.00027