Ann Surg Oncol (2022) 29:4033–4036
https://doi.org/10.1245/s10434-022-11588-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – SARCOMA

Good Bone Structure: A Call for Stronger Design and Methodology in Disparities Studies in Orthopedic Oncology

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In their study 'Non-private health insurance predicts advanced stage at presentation and amputation in lower extremity high grade bone sarcoma: a National Cancer Database study', Jawad et al. aim to identify factors associated with amputation and stage at presentation for patients with bone sarcomas, as well as the impact of amputation on survival across age groups.[1] They attempt to explore the relationship between health insurance status and these outcomes in a broad orthopedic oncology population that encompasses osteosarcoma, Ewing sarcoma, chondrosarcoma, and malignant giant cell tumors in patients of all ages.

This subject is particularly challenging to examine, since the relationship between cancer care outcomes and health insurance in the United States is nuanced and complex. Insurance status does not drive oncologic outcomes in a silo; it is both reflective of and independently associated with other factors that lead to disparate outcomes. Exploring these factors becomes more challenging in a large database such as the National Cancer Database (NCDB), where explicit measures of the real-world variables that we know contribute to disparate outcomes are elusive and we rely heavily on surrogate measures. However, while the NCDB lacks granularity for certain variables, it captures over 72% of cancer cases across the country each year and therefore remains a valuable resource for examining population-level outcomes data.[2] This is particularly true of rare diseases, for which large institutional cohort studies may not be feasible. A particularly useful aspect of the NCDB is its capacity to explore population-level trends in practice patterns and outcomes before and after landmark societal changes, such as the implementation of the Affordable Care Act (ACA) in 2010. Approached in a thoughtful way, the NCDB and other databases may have an important role in identifying whether policy changes related to items such as insurance status are associated with changes in treatment approaches and outcomes in oncology.

Although the subject of this study is important, a number of methodologic failures limit the value of the authors' examination of factors predicting amputation and survival in high-grade bone sarcomas. As would be expected, when dividing the study population into patients who underwent amputation versus limb-sparing surgery (LSS) and patients with stage I–III disease versus stage IV disease, there was substantial heterogeneity between patient populations. In this study, this heterogeneity was predictably observed within variables that have been previously demonstrated to have an association with overall survival (OS) or the need for amputation, including histology, primary tumor site, tumor grade, margin status, and community treatment center. However, it is important to note that the authors incorrectly reference these statistically significant tests of heterogeneity within their surgical and staged populations as statistically significant *predictors* of surgical extent and stage at presentation; this is not supported by the statistical analyses reported in their supplementary data.[1] In particular, they emphasize a disproportional impact of amputation on survival in pediatric and adolescent/young adult (AYA) patients compared with older adults, but did not conduct a multivariate analysis that included both age groups. They do report a greater difference in survival

First Received: 24 February 2022
Accepted: 27 February 2022;
Published Online: 4 April 2022

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between patients undergoing LSS versus amputation for pediatric and AYA patients (10-year OS of 65% after LSS vs. 47% after amputation) compared with older adults (10-year OS of 39% after LSS vs. 28% after amputation), but these age groups were analyzed separately, not in a multivariate model that accounted for age or histology. In their Kaplan–Meier curves in Fig. 1, there actually seems to be an approximately proportionate difference between LSS and amputation for both the pediatric/AYA and adult age groups. Furthermore, the higher mortality rate observed in the older populations irrespective of the surgery performed suggests that any difference identified may simply be driven by age, a phenomenon that has already been observed for osteosarcoma and Ewing sarcoma.

The multivariate regression results for variables that *are* included are somewhat devalued by the way in which the multivariate models were constructed, whereby the least clinically intuitive groups or the groups with the fewest patients were elected as the reference groups; for example, 'other' race (17 patients) or Charlson comorbidity score of 3+ (21 patients). These modeling decisions make it challenging to statistically adjust for other variables with meaningful results. Additionally, a 49% survival statistic for the overall population at 5 years, with only an additional 2% of patients ($N = 116$) dying by 10 years (10-year OS was 49%), suggests some inherent issues with either the data or the analysis. However, the most prominent design and methodologic flaws in this study are (1) the heterogeneity of the included histologies; (2) the conversion of insurance status into a binary variable that inherently contradicts the final conclusion; and (3) the authors' definitions of amputation versus LSS.

Osteosarcoma, chondrosarcoma, Ewing sarcoma, and malignant giant cell tumors of bone vary substantially in their age at presentation, behavior, and treatment approach. Chemotherapy is a pillar of therapy for Ewing sarcoma and osteosarcoma, which typically includes both neoadjuvant and adjuvant therapy in addition to a wide surgical resection as standard of care.[3,4] Conversely, chondrosarcoma is largely a surgical disease, and a malignant giant-cell tumor of bone does not fit neatly into any standard treatment paradigm due to its rarity.[3,4] The application of radiation in bone sarcomas also varies widely based on histology, as well as other characteristics such as margin status, tumor grade, tumor size, and anticipated technical resectability. Histology-specific analyses for rare tumors are feasible with the NCDB, and indeed, this capacity is one of the great strengths of such a large database, but the authors did not attempt these analyses. As with much of our retrospective sarcoma literature, failure to evaluate histology-specific treatment approaches leaves us with conclusions that are neither easily interpretable nor generalizable.

With respect to the authors' investigation of the impact of insurance status, although insurance status was positively associated with amputation and advanced stage at presentation on their multivariate analysis, their rationale for re-categorizing insurance status as a binary variable provokes some concern about the strength of their conclusions: in constructing a binary insurance variable, they group patients with Medicare coverage and private insurance together and then patients with no insurance and Medicaid coverage together. The rationale provided for this is that 'patients presenting with no insurance to a healthcare facility are enrolled in Medicaid'. First, this is not uniformly true, and, second, eliminating the distinction

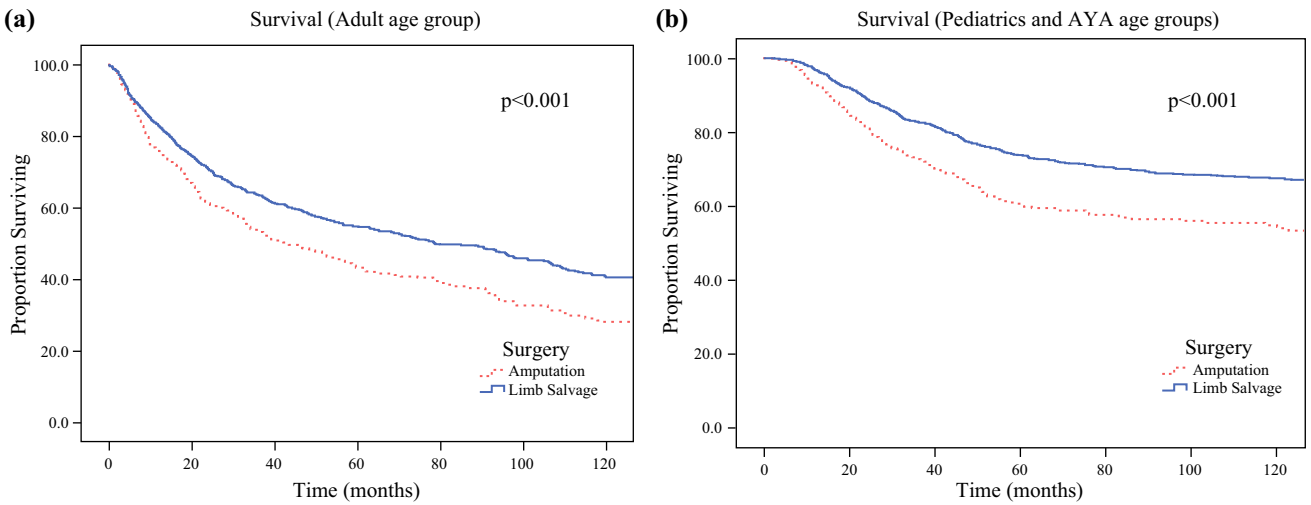

FIG. 1 Kaplan-Meier curves from Jawad et al. study showing overall survival for amputation versus limb salvage for (**a**) adults and (**b**) pediatric and AYA age group. Retrieved from Jawad et al.[1]

between uninsured patients and those with Medicaid coverage robs us of the opportunity to explore how the expansion of eligibility for Medicaid has influenced the number of cancer patients who may have benefited from this coverage since 2010. Finally, while the title of their study alludes to an examination of the influence of non-private insurance on outcomes, both of their constructed insurance categories include non-private (government-funded) health insurance in the form of Medicare or Medicaid.

Finally, the authors' surgical categorization is difficult to interpret. In their supplementary Table 1, which summarizes the baseline patient characteristics, the authors report that 79.6% of patients had an LSS, while 20.4% had an amputation. However, they report only 59.5% of patients in the study population had a 'radical resection' as their limb-sparing operation. While Current Procedural Terminology (CPT) coding distinguishes radical resection from wide excision among limb-sparing procedures, the NCDB 2017 participant user file (PUF) 'radical resection' code encompasses both radical resections and wide excisions.[5] Thus, in an NCDB study, any LSS other than a 'radical resection' for lower extremity sarcoma equates to a partial resection or local excision. If only 59.5% of the study population had a radical resection, then it would seem 20.1% of patients in the study population (1162 patients) had an LSS that may have amounted to nothing more than an incomplete/partial resection or an incisional or excisional biopsy. Furthermore, it is challenging to reconcile a 59.5% radical resection rate with the 92.4% margin-negative resection rate that the authors report.[1] Ultimately, it is difficult to draw any conclusions about the impact of LSS on survival when the very intervention being studied is not clearly defined and the indication for surgery seems to span anything from diagnosis to curative-intent treatment to palliation.

Jawad et al. have explored an important topic in orthopedic oncology. Unfortunately, their study reports flawed results and suffers from a reductionist approach that fails to account for important interactions within and between cancer characteristics and sociodemographic factors that may contribute to disparate outcomes in this patient population. Particularly troublesome in their study design is the categorical supposition that any patient without insurance is enrolled in Medicaid upon hospital presentation. Eligibility criteria for Medicaid vary from state to state and policies ensuring Medicaid enrollment for uninsured patients are not established uniformly, or even commonly, across the country. While such policies would certainly benefit patients in the United States by mitigating some of the financial burden associated with their cancer care, designing a study based on the incorrect assumption that all cancer patients leave hospital with government-funded insurance undermines the struggle of millions of uninsured patients. Similarly, the authors denote that "[d]etermination of modifiable factors impacting amputation is critical to developing strategies designed to increase the feasibility of limb salvage procedures", but go on to describe associations between amputation and a myriad of non-modifiable risk factors such as age, race, socioeconomic status, tumor biology, education, and insurance status. Insurance status in the United States is not a modifiable risk factor; insurance-related disparities cannot be overcome with a 'lack-of-insurance' cessation program. Risk factors related to insurance status, such as financial insecurity and inequitable access to timely diagnosis and treatment, are only modifiable at a policy level, and even (especially) then, present a monumentally complex problem.

Exploring disparities in oncology requires a more thoughtful and regimented approach than is observed in much of the literature. The conceptualization and design of disparities studies in oncology must be undertaken with significant appreciation and scrutiny of the numerous sociodemographic factors, cancer characteristics, and treatment approaches that are implicated in cancer outcomes. The web of sociodemographic factors that contribute to disparities in cancer care, including but not limited to race, sex, sexual orientation, age, ability, socioeconomic status, insurance status, and geography, is dense and complex. Similarly, the impact of cancer characteristics such as tumor grade, local or distant spread, the presence of biomarkers, and chemo- or radiosensitivity constitutes another layer of complexity. Furthermore, the rapid pace of scientific discovery, varying institutional experiences, and limits in information and data dissemination may affect treatment decisions and outcomes for cancer patients across institutions. The resulting collective relationship then, between all of these variables, is an inherent landmine of confounding if not approached with thoughtfulness, humility, and methodologic rigor. This is perhaps most relevant to rare malignancies such as bone sarcomas, since, with centralization of care, factors such as rurality and the cost of travel may impact stage at presentation, timeliness of treatment, and consistency of follow-up more profoundly than in common tumors managed at community sites.

The manuscript by Jawad et al. reinforces that the study of disparities in cancer care is challenging and complex. Their study shines a light on the importance of cultivating studies that are designed to explore disparities in a rigorous way with the potential to add value to the body of literature in this field.

DISCLOSURE Alexandra C. Istl, Carol D. Morris, and Fabian M. Johnston declare no conflicts of interest.

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