The burden of skeletal-related events in four Latin American countries: Argentina, Brazil, Colombia, and Mexico

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ABSTRACT

Aim: Skeletal-related events (SREs) are major bone complications that frequently occur in patients with solid tumors (ST) and bone metastases, and in patients with multiple myeloma (MM). SREs include pathological fracture, spinal cord compression, radiation to bone, and surgery to bone. Limited data are available regarding the burden of SREs in Latin America. We built an economic model to quantify the current and future economic burden of SREs among adults in four Latin American countries: Argentina, Brazil, Colombia, and Mexico.

Methods: A comprehensive literature review with a systematic search strategy was conducted to parameterize the economic burden of illness (BOI) model. Economic analyses were conducted using a prevalence-based model. Aggregate SRE costs obtained from country-specific sources were used. We also included patient productivity losses. Costs were expressed in 2020 USD for the total annual burden, annual burden per 1,000 at risk, and projected five-year burden.

Results: The estimated total number of SREs was 251,503 in 2020, amounting to a total annual cost of USD 1.4 billion. The total projected five-year cost was USD 6.9 billion. Annual costs were highest in Brazil (USD 779.1 million), followed by Mexico (USD 281.8 million), Argentina (USD 174.6 million), and Colombia (USD 120.1 million). The average financial burden per 1,000 at risk was greatest in Brazil (USD 3.6 million), followed by Mexico (USD 3.4 million), Colombia (USD 2.9 million), and Argentina (USD 2.7 million).

Conclusion: Despite recommendations by medical societies for the use of bone-targeted agents in patients with solid tumors and bone metastasis or with multiple myeloma and bone lesions, a large proportion of patients at risk of experiencing SREs are not treated. Early detection of bone metastases and SREs and the use of the most effective preventative treatments are needed to decrease the clinical and economic burden of SREs in Latin America.

Introduction

Bone is one of the most common sites of metastasis among patients with solid tumor (ST) cancers. Up to 75% of patients with advanced prostate or breast cancer will develop bone metastases during the course of their disease. Given that patients with breast or prostate cancer have a relatively long survival time after diagnosis of bone metastases, the prevalence of bone metastases is high. For other types of ST cancers, such as lung, bladder, kidney, thyroid, and melanoma, the incidence of bone metastases with advanced disease ranges from 14 to 60%.

Multiple myeloma (MM) is an aggressive cancer of the bone marrow plasma cells and is also characterized by lytic bone lesions. Approximately 90% of patients with MM will develop lytic bone lesions during the course of their disease. Patients with ST and bone metastases or MM are highly susceptible to bone complications known as skeletal-related events (SREs). SREs include pathologic fractures, spinal cord compression, radiation to bone, and surgery to bone. Up to 64% of patients with ST and bone metastases, and up to 95% of patients with MM and lytic bone lesions will experience an SRE over the course of their disease.

All SREs are associated with pain progression, impaired quality of life, and an increased risk of death. Based on the critical and potentially fatal effects of SREs, it is important to seek effective preventative options.

Bone-targeted agents (BTA) are recognized as the current standard of care for treating bone metastases and preventing SREs. Following the diagnosis of bone metastases, it is recommended to initiate BTA, such as zoledronic acid (a bisphosphonate) or denosumab (a human monoclonal antibody against RANKL). A study investigating the use of...
intravenous bisphosphonates in patients with bone metastases secondary to breast, lung, or prostate cancer reported that discontinuation rates remain high in clinical practice. A phase III clinical trial demonstrated that, despite receiving zoledronic acid, 36–39% of patients with bone metastases secondary to ST still experienced at least one SRE during the 21 months of treatment. A recent meta-analysis that included three large phase 3 trials (one trial in prostate cancer, one in breast cancer, and one in other ST and MM) and compared denosumab vs. zoledronic acid for the prevention of pathological fracture in patients with bone metastases from advanced cancer concluded that denosumab reduces the likelihood of pathological fractures compared to zoledronic acid (odds ratio [OR] 0.86; 95% confidence interval [CI], 0.74–0.99; p = .04). The main end-point for the randomized controlled trials (RCTs) included in this meta-analysis was the first on-study SRE. Denosumab was demonstrated to be superior to zoledronic acid in patients with prostate cancer (hazard ratio [HR], 0.82 [95% CI, 0.71–0.95; p = .008]) and patients with breast cancer (HR, 0.82 [95% CI, 0.71–0.95; p = .01]) and non-inferior to zoledronic acid in patients with other ST (i.e. not breast or prostate cancer) or MM (HR, 0.84 [95% CI, 0.71–0.98; p = .0007]) in delaying time to first on-study SRE. SREs represent an economic burden to society due to the associated increased health care resource utilization and costs. Patients with bone metastases and SREs incur significantly higher medical care costs than patients without SREs. Based on an observational European study, 21–48% of patients with SREs require an inpatient hospital stay with an average duration ranging from 8.4 to 41.1 days. SREs are also associated with numerous diagnostic tests, procedures, and outpatient visits. Direct health care costs (i.e. inpatient stays, outpatient visits, home/long-term care, facility stays, daycare visits, emergency room visits, and procedures) for SREs in patients with ST and bone metastases in Europe range from €704 to €51,186, while the per-patient-per-year cost for an SRE in patients with MM can be up to $80,000 in United States dollars (USD). Furthermore, a retrospective study based in the United States (US) showed that 67% of patients with SREs experienced disability or the inability to complete daily routine tasks, and 35% lost their jobs due to the physical inability to complete work functions. Loss of income due to patients’ inability to work can have detrimental financial impacts on patients and their families.

While the burden of SREs has been well-defined in the US and several European countries, this burden is not well-understood in Latin America. Therefore, the objective of this study was to determine the economic burden of SREs in Latin American countries: Brazil, Mexico, Colombia, and Argentina.

**Methods**

**Comprehensive literature review**

We conducted a comprehensive literature review to collect relevant evidence for the four Latin American countries of interest: Argentina, Brazil, Colombia, and Mexico. Our population of interest was adults (≥18 years old) with ST with bone metastases and SREs, or with MM and SREs. We sought information on the prevalence and incidence of SREs in patients with ST with bone metastasis, and in patients with MM with lytic bone lesions, as well as the associated economic burden (e.g. health care resource utilization, direct health care costs, and indirect/societal costs). We did not limit study selection by study design, or by intervention or comparators. We focused on literature published in English, Spanish, and Portuguese from 1 January 2010 to 5 September 2019. An experienced medical information specialist developed and tested the search strategy, which was also peer-reviewed by another senior information specialist using the Peer Review of Electronic Search Strategies (PRESS) Checklist. Using the OVID platform, we searched Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS Economic Evaluation Database, and the Cochrane Central Register of Controlled Trials. We also undertook a search of four relevant Latin American databases: LILACS, Scielo, BVS, and Redalyc (see Supplementary Appendix S1). We performed grey literature searches using a modified version of the tool Grey Matters: a practical tool for searching health-related grey literature (see Supplementary Appendix S2), as well as targeted searches for relevant data from other countries.

**Key opinion leader interviews**

Between November 2019 and March 2020, we conducted interviews with one oncologist and one hematologist from each country of interest to supplement the literature review.

**Burden of illness model**

A prevalence-based burden of illness (BOI) model was built for Argentina, Brazil, Colombia, and Mexico using data collected in our comprehensive literature review, targeted literature searches, and key opinion leader (KOL) interviews (i.e. interviews with oncologists and hematologists). Wherever possible, country-specific inputs were used to parameterize the BOI model. Costs are presented in 2020 US dollars (USD). Currencies were converted using exchange rates effective 24 March 2020. The population of interest was split into four patient groups: prostate cancer, breast cancer, other solid tumors, and MM.

**Epidemiology of skeletal-related events**

To calculate the annual number of pathological fractures, radiation to bone, spinal cord compressions, and surgeries to the bone for each patient group (prostate cancer, breast cancer, other solid tumors, and MM) in each country, we used estimates of the prevalence of patients with bone metastases from prostate cancer, breast cancer, and other solid tumors, and the prevalence of patients with MM and bone lesions, along with the annual rates of SREs for each group.
**Prevalence of prostate cancer, breast cancer, and other solid tumors**

To estimate the prevalence of patients with ST (prostate cancer, breast cancer, and other solid tumors) and bone metastasis, we followed the method described by Cristino et al.\(^{39}\) using country-specific mortality rates reported by the Institute for Health Metrics and Evaluation\(^{40}\). The method described by Cristino et al. assumes that annual cancer mortality is equal to the annual incidence of metastatic disease. For solid tumors, the annual mortality rate was obtained by subtracting the annual mortality rate of breast cancer, prostate cancer, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and MM from the overall cancer mortality rate in each country. Based on data from Coleman\(^1\), we assumed that 70% of patients who die of prostate or breast cancer, and 35% (median value reported for tumors other than prostate and breast by Coleman\(^1\)) of patients who die of other solid tumors have bone metastasis. These mortalities were assumed as the annual incidence of patients with ST and bone metastasis. Lastly, we estimated the prevalence of patients with ST and bone metastasis as the multiplication of the annual incidence by mean survival time (prevalence = incidence × survival), consistent with the method described by Cristino et al.\(^{39}\). Values obtained from published literature for mean survival time were 2.24, 3.73, and 1.73 years for prostate cancer, breast cancer, and other solid tumors, respectively\(^41,42\). See Table 1 for the calculation of the prevalence of ST and bone metastasis.

**Prevalence of multiple myeloma**

No country-specific data were identified to inform the total prevalence of MM in the Latin American countries of interest. To estimate the total prevalence of MM in Argentina, Brazil, Colombia, and Mexico, we calculated the ratio of MM prevalence between the United States (US) and each of the Latin American countries by using the country-specific 5-year prevalence reported by the World Health Organization\(^{43}\). Then, we used the calculated ratios (US prevalence to Latin American country prevalence) to estimate the MM prevalence in our countries of interest-based on the prevalence of MM in the US reported by the National Cancer Institute in 2016\(^{44}\). Estimated Latin American prevalent cases were extrapolated to 2020 values based on population growth\(^45\). Lastly, we assumed that 86.4% of patients with MM have lytic bone lesions as reported by Hungria et al.\(^{46}\). See Table 2 for the calculation of the prevalence of MM with lytic bone lesions.

### Table 1. Prevalence of solid tumors with bone metastasis.

|                | Argentina | Brazil | Colombia | Mexico |
|----------------|-----------|--------|----------|--------|
|                | Prostate cancer | Breast cancer | OSTs | Prostate cancer | Breast cancer | OSTs | Prostate cancer | Breast cancer | OSTs | Prostate cancer | Breast cancer | OSTs |
| Annual mortality\(^a\) (n) | 4,938 | 6,778 | 58,859 | 19,712 | 18,818 | 188,625 | 3,743 | 3,385 | 35,112 | 7,556 | 7,776 | 73,223 |
| Proportion with BM\(^1\) | 70% | 70% | 35% | 70% | 70% | 35% | 70% | 70% | 35% | 70% | 70% | 35% |
| Mortality with BM (n)\(^b\) (assumed equal to incidence of cancer with BM) | 3,457 | 4,744 | 20,601 | 13,798 | 13,172 | 66,019 | 2,620 | 2,369 | 12,289 | 5,289 | 5,443 | 25,628 |
| Survival (years)\(^{41,42}\) | 2.24 | 3.73 | 1.73 | 2.24 | 3.73 | 1.73 | 2.24 | 3.73 | 1.73 | 2.24 | 3.73 | 1.73 |
| Prevalence of cancer with BM (n)\(^{41,42}\) (incidence × survival) | 7,743 | 17,697 | 35,639 | 30,908 | 49,133 | 114,212 | 5,869 | 8,838 | 21,260 | 11,848 | 20,302 | 44,337 |

*Abbreviations: BM, bone metastasis; OST, other solid tumors.

\(^a\)Estimated mortality for 2020. Based on mortality rates\(^40\) and population data from the World Bank Group (https://databank.worldbank.org).

### Table 2. Prevalence of multiple myeloma with lytic bone lesions.

|                | Argentina | Brazil | Colombia | Mexico |
|----------------|-----------|--------|----------|--------|
| (i) Ratio of MM prevalence in US to MM prevalence in LATAM country\(^a\) | 28.8 | 5.4 | 23.6 | 18.05 |
| (ii) Total prevalent cases in US in 2016\(^{44}\) | 131,392 | 131,392 | 131,392 | 131,392 |
| Total prevalent cases in LATAM country in 2016 (ii/i) | 4,562 | 24,332 | 5,567 | 7,279 |
| Estimated prevalence for LATAM country in 2020\(^b\) | 4,754 | 25,124 | 5,910 | 7,623 |
| Proportion with lytic bone lesions\(^{46}\) | 86.4% | 86.4% | 86.4% | 86.4% |
| Estimated prevalence of MM with lytic bone lesions (2020) | 4,108 | 21,707 | 5,106 | 6,587 |

*Abbreviations. LATAM, Latin-America; MM, multiple myeloma; US, United States.

\(^a\)5-year prevalence in US/5-year prevalence in the respective LATAM country (i.e. Argentina, Brazil, Colombia, or Mexico)\(^{43}\).

\(^b\)Based on population growth (https://databank.worldbank.org).
were informed by unpublished data from four clinical trials of denosumab vs. zoledronic acid\textsuperscript{15,16,19,48}. SRE rates were calculated as the incidence of SREs divided by follow-up time (subject-years). Relative risk (RR) for incidence of SREs in patients treated with bisphosphonates vs. no treatment were obtained from three Cochrane reviews\textsuperscript{49–51} and used to estimate annual SRE rates for untreated patients. Macherey et al.\textsuperscript{51}, O’Carriagan et al.\textsuperscript{52}, and Mhaskar et al.\textsuperscript{50} reported RRs for overall SRE incidence of 0.87 for patients with prostate cancer, 0.85 for patients with breast cancer, and 0.74 for patients with MM, respectively, in patients treated with bisphosphonates vs. no treatment.

**Skeletal-related events management cost**

Aggregate SRE management costs were obtained from country-specific sources. Costs for Colombia were obtained from the budget impact analysis (BIA) (Colombian healthcare system’s perspective) published by Pérez et al.\textsuperscript{52} and inflated to 2020 values using the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) Cost Converter\textsuperscript{53}. Costs for Brazil were informed by the BIA (private healthcare system’s perspective) published by Tanaka et al.\textsuperscript{54}. Details of sensitivity analysis for Brazil using alternative costs from the public healthcare system are provided in Supplementary Appendix S3. Costs for Mexico were informed by data from the Instituto Mexicano del Seguro Social (Mexican Social Security Institute)\textsuperscript{55,56}. Costs for Argentina were informed by KOL feedback on medical resource utilization and costs from the Programa de Atención Médica Integral (Comprehensive Medical Care Program).\textsuperscript{57} Data sources for Argentina and Brazil split costs into two groups: (i) costs for patients with prostate cancer, breast cancer, or MM, and (ii) cost for patients with other solid tumors. For Colombia and Mexico, the same aggregate costs for each SRE were reported across all types of cancer. See Table 3 for SRE management costs.

**Productivity loss associated with skeletal-related events**

Productivity loss associated with SREs was mainly informed by KOL feedback due to a lack of published literature on this topic. See Supplementary Appendix S4 for a summary of the methods and inputs that were used to estimate productivity loss.

**Economic burden of SREs**

To estimate the economic burden of SREs, we multiplied the annual rates of SREs by the estimates of patients at risk (patients with ST and bone metastasis, and patients with MM and lytic bone lesions) to obtain the annual number of SREs for each country. Next, we multiplied the country-specific SRE management costs by the estimated annual number of SREs. Lastly, we added the costs associated with productivity loss to the total economic burden for each country.

**Results**

We screened 2,486 records identified through database searching (MEDLINE, Embase, Cochrane, LILACS, Scielo, BV5, Redalyc). Including 20 records identified through additional grey literature and targeted searches, 26 sources of data were included for informing the BOI model.

The BOI model predicted 251,503 SREs would occur in 2020 in the four Latin American countries analyzed, based on prevalence of disease (Table 1, 2) and rates of SREs (unpublished data)\textsuperscript{15,16,19,48}. Expected cases were highest for Brazil (total number: 133,653; annual incidence: 0.63 per 1,000), followed by Mexico (total number: 51,972; annual incidence: 0.40 per 1,000), Argentina (total number: 39,653; annual incidence: 0.87 per 1,000), and Colombia (total number: 26,254; annual incidence: 0.51 per 1,000).

Table 4 depicts the annual (2020) BOI of SREs in the analyzed countries (see Table 3 for SRE management costs). In Brazil, the largest expenditure was radiation to bone (60.7% of burden), followed by vertebral fracture (18.1% of burden), and non-vertebral fracture (14% of burden). In Mexico, the largest expenditure was radiation to bone (46.2% of burden), followed by spinal cord compression (18.7% of burden), and non-vertebral fracture (12.9% of burden). In Argentina, the largest expenditure was radiation to bone (54.4% of burden), followed by non-vertebral fracture (17% of burden) and vertebral fracture (15.5% of burden). In Colombia, the largest expenditure was vertebral fracture (31% of burden), followed by non-vertebral fracture (27.9% of burden), and radiation to bone (24.5% of burden).

Table 5 shows the annual BOI of SREs stratified by type of cancer (prostate cancer, breast cancer, other solid tumors, and MM). Other ST constituted ~62% of the total BOI for the four Latin American countries analyzed, prostate cancer (16%) and breast cancer (17%) together constituted approximately a third of the burden, and MM constituted 6% of the burden. These proportions were relatively similar across the four countries for the BOI of SREs associated with other ST (range from 55% [Colombia] to 64% [Mexico]), prostate cancer (range from 13% [Argentina] to 16% [Brazil and Mexico]), and breast cancer (range from 15% [Mexico] to 19% [Argentina]). A greater variation was observed for the BOI associated with MM: 4, 6, 12, and 5% of the total BOI for Argentina, Brazil, Colombia, and Mexico, respectively. The greater relative BOI of SREs associated with MM in Colombia (12 vs. 4–6% in other countries) is mainly explained by two factors: (i) higher rates of fractures and lower rates of radiation to bone among patients with MM compared to ST, and (ii) a higher ratio fracture cost to radiation cost in Colombia than in Argentina, Brazil, and Mexico (Table 3).

As the countries included in this study have different population sizes, comparing the burden per 1,000 at risk provided more meaningful insight into the differences in per-patient expenditures in these countries. The average burden per 1,000 at risk in Latin America was USD 3,150,673. The country with the greatest burden was Brazil (USD 3,607,528), followed by Mexico (USD 3,392,247), Colombia (USD 2,924,375), and Argentina (USD 2,678,544) (Figure 1).
When the four Latin American countries were considered together, the one-year (2020) BOI was USD 1.4 billion, and the projected five-year BOI was USD 6.9 billion. The country that contributed most to the burden was Brazil, followed by Mexico, Argentina, and Colombia. As expected, Brazil and Mexico contributed the most as they have the largest populations (212,871,096 and 129,164,010, respectively [2020]) and the greatest standardized costs (per 1,000 at risk) for SRE management. Although Argentina has a smaller population compared to Colombia (45,426,785 and 51,131,075, respectively [2020]) and the standardized cost for SRE management in Argentina is lower than in Colombia, its contribution to the total burden is greater than Colombia’s contribution due to a greater prevalence of patients with solid tumors and bone metastasis (Table 1).

**Discussion**

This BOI model demonstrates that SREs are associated with a substantial economic burden in Argentina, Brazil, Colombia, and Mexico. The estimated total number of SREs is 251,503...
in 2020, resulting in a total annual cost of approximately USD 1.4 billion, and a projected economic burden of USD 6.9 billion over the next five years. Both pathological fracture (vertebral and non-vertebral) and radiation to bone each accounted for \( \approx 45\% \) of the total number of SREs (and together accounted for almost 90\% of total SREs).

The relative costs for the different types of SREs varied across countries. For instance, from the five types of SREs that we considered (vertebral fracture, non-vertebral fracture, radiation to bone, surgery to bone, and spinal cord compression), radiation to bone was the least expensive SRE in Colombia, the second and third most expensive SRE in

### Table 5. One-year burden of illness of SRE in Argentina, Brazil, Colombia, and Mexico stratified by type of cancer.

| Cost category       | Argentina $ ( % ) | Brazil $ ( % ) | Colombia $ ( % ) | Mexico $ ( % ) | Total LATAM $ ( % ) |
|---------------------|-------------------|----------------|------------------|----------------|---------------------|
| Vertebral fracture  | 27,061,296 (100)  | 140,855,041 (100) | 37,223,768 (100)  | 31,318,732 (100)  | 236,458,837 (100)  |
| Prostate cancer     | 3,487,435 (13)    | 22,237,947 (16)  | 5,865,856 (16)    | 4,099,724 (16)    | 36,500,962 (15)    |
| Breast cancer       | 7,783,294 (29)    | 32,707,088 (23)  | 8,005,311 (22)    | 7,852,960 (25)    | 65,350,643 (24)    |
| Other ST            | 12,899,043 (48)   | 62,645,710 (44)  | 16,203,989 (44)   | 14,600,785 (46)   | 106,359,226 (45)   |
| MM                  | 2,891,524 (11)    | 12,208,318 (11)  | 3,745,584 (11)    | 3,909,724 (14)    | 22,517,666 (11)    |
| Non-vertebral fracture | 29,705,304 (100) | 109,433,597 (100) | 33,536,449 (100)  | 36,363,098 (100)  | 209,038,449 (100)  |
| Prostate cancer     | 2,615,577 (9)     | 12,208,318 (11)  | 3,745,584 (11)    | 3,909,724 (14)    | 22,517,666 (11)    |
| Breast cancer       | 9,852,661 (33)    | 32,709,078 (23)  | 8,005,311 (22)    | 7,852,960 (25)    | 59,447,106 (28)    |
| Other ST            | 14,829,303 (50)   | 52,738,396 (48)  | 16,203,989 (44)   | 14,600,785 (46)   | 106,239,526 (45)   |
| Radiation to bone   | 94,995,836 (100)  | 472,545,159 (100) | 29,389,300 (100)  | 130,234,653 (100) | 727,164,949 (100)  |
| Prostate cancer     | 14,092,302 (15)   | 84,304,254 (18)  | 5,299,389 (18)    | 22,687,237 (17)   | 126,349,003 (17)   |
| Breast cancer       | 13,853,050 (15)   | 57,972,389 (12)  | 3,484,748 (12)    | 16,887,873 (13)   | 92,198,059 (13)    |
| Other ST            | 66,260,108 (70)   | 323,530,105 (68) | 20,148,090 (69)   | 89,274,784 (69)   | 499,213,087 (69)   |
| Spinal cord compression | 10,608,735 (100) | 17,408,107 (100) | 9,749,707 (100)   | 57,748,784 (100)  | 90,518,909 (100)   |
| Prostate cancer     | 2,046,114 (19)    | 4,141,139 (24)   | 2,337,689 (24)    | 11,939,081 (23)   | 20,464,024 (24)    |
| Breast cancer       | 866,085 (8)       | 11,856,569 (68)  | 6,693,165 (69)    | 36,751,065 (70)   | 62,957,469 (75)    |
| Other ST            | 7,627,651 (72)    | 182,964 (1)      | 117,355 (1)       | 408,863 (1)       | 778,066 (1)        |
| Radiation to bone   | 11,523,001 (100)  | 23,140,439 (100) | 9,112,997 (100)   | 25,565,502 (100)  | 69,341,939 (100)   |
| Prostate cancer     | 426,263 (4)       | 1,132,448 (5)    | 468,081 (5)       | 1,219,427 (5)     | 3,246,219 (5)      |
| Breast cancer       | 1,562,910 (14)    | 2,686,726 (12)   | 948,479 (10)      | 3,060,075 (12)    | 8,260,190 (12)     |
| Other ST            | 8,826,955 (77)    | 16,983,244 (73)  | 6,644,151 (73)    | 19,338,117 (76)   | 51,792,468 (75)    |
| Spinal cord compression | 706,873 (6)       | 2,336,021 (10)   | 1,052,285 (12)    | 1,947,828 (8)     | 6,043,061 (9)      |
| Prostate cancer     | 710,355 (100)     | 15,702,107 (100) | 1,099,437 (100)   | 5,571,418 (100)   | 23,837,317 (100)   |
| Breast cancer       | 56,936 (8)        | 2,178,026 (14)   | 34,468 (3)        | 591,565 (11)      | 2,860,995 (12)     |
| Other ST            | 55,969 (8)        | 2,512,407 (16)   | 40,178 (4)        | 574,099 (10)      | 3,182,653 (14)     |
| Radiation to bone   | 324,801 (46)      | 1,594,264 (10)   | 891,700 (81)      | 1,790,147 (32)    | 5,600,912 (20)     |

Abbreviations. LATAM, Latin America; MM, multiple myeloma; ST, solid tumors; SRE, skeletal-related event.

**Figure 1.** Burden of illness of SREs per 1,000 at risk in Argentina, Brazil, Colombia, and Mexico.
Argentina and Mexico, respectively, and the most expensive SRE in Brazil. Likewise, a vertebral fracture was the second most expensive SRE for both Brazil and Colombia, and the fourth most expensive for both Argentina and Mexico (see Table 3 for SRE management costs).

In terms of the contribution of different types of SREs to the total economic burden, for Argentina, Brazil, and Mexico, the highest proportion of the economic burden was from radiation to bone (54, 61, and 46%, respectively), followed by non-vertebral fracture in Argentina (17%), vertebral fracture in Brazil (18%), and spinal cord compression in Mexico (19%). For Colombia, the highest proportion of the economic burden was from vertebral fracture (31%), followed by non-vertebral fracture (28%).

Variation in SRE-associated costs across countries has been reported in Europe. A cost of illness analysis in Austria, the Czech Republic, Finland, Greece, Portugal, and Sweden noted variations in the mean SRE-associated costs across countries (even with adjustment for purchasing power parity). The authors stated that cost differences were likely driven by differences in both unit costs and treatment practices across countries. The use of less invasive surgical procedures in countries, such as Finland and Portugal has been noted as a potential variation in treatment practices that may impact the healthcare resource utilization costs associated with SREs.

Despite recommendations for the initiation of a bisphosphonate or denosumab at the time of diagnosis of bone metastasis to prevent or delay the first or subsequent bone complications, unmet needs remain about the proportion of patients with the malignant bone disease treated with BTA. A European cost of illness study reported that 60% of patients with bone metastases or lesions secondary to breast cancer, prostate cancer, lung cancer, or multiple myeloma did not receive BTA. Of the patients who experienced an SRE, 37% remained untreated. A large chart-review study conducted in France, Germany, Italy, Spain, and the United Kingdom found that 44% of patients with lung cancer and bone metastases were not receiving BTA, and 23% were predicted never to receive them. Based on KOL feedback, we estimated that most patients with ST and bone metastasis in Brazil, Colombia, and Mexico do not receive treatment for the prevention of SREs (55, 70, and 54%, respectively). Likewise, local market research in Argentina determined that 35% of these patients remain untreated. Early detection of bone metastases and SREs and the use of the most effective preventative treatments are needed to decrease the economic burden of SREs and prevent the worsening of patient quality of life.

A limitation of this study is that our estimates of SRE burden used data from clinical trials that implemented skeletal surveys for fracture assessment. Carter et al. stated that the use of frequent clinical trial skeletal surveillance may result in overestimation of SREs compared to a real-world treatment scenario, mainly due to the identification of asymptomatic vertebral fractures that would not ordinarily be noticed in regular clinical settings. Liao et al. conducted a retrospective chart review study to ascertain if the proportion of patients with metastatic breast cancer who had an SRE in a sample of patients in routine clinical practice was comparable to that seen in phase III RCTs of bisphosphonate therapy. The authors found that the proportion of patients reported to experience an SRE in routine clinical practice was 30.2% lower compared with the incidence of SREs observed in the treatment arm of RCTs of intravenous bisphosphonates (30 vs. 43%). Since clinical trial data were used to inform the burden on SREs in this study, there is the risk of potential overestimation of the BOI. For our study, the lack of data on SRE rates in Latin America hampered the estimates of country-specific SRE burden.

Several publications based on real-world data have confirmed the substantial burden associated with SREs in Europe. SREs are associated with significant healthcare resource utilization related to an increase in the frequency and length of hospitalizations, as well as in the number of medical procedures and outpatient, emergency room, and day-care hospital visits. Developing countries (including Latin American countries) may face limitations in health care access, which may result in a relatively lower rate of medical procedures (including those classified as SREs, such as radiation to bone or surgery to bone, and those used to treat SREs) compared to developed countries. However, limitations in health care access for patients with SREs would likely be associated with other sources of burden that were not captured in this study, including pain and loss of mobility and independence, and associated costs. Future studies should seek to determine the potential impact of care patterns on the burden of SREs in Latin America.

To our knowledge, this is the first study aimed at quantifying the economic burden of SREs in Latin America. We conducted a comprehensive literature review to find the most relevant data to our BOI model. The model took into account the expected differences in rates of SREs for patients who are treated vs. not treated for prevention of SREs. As part of the model inputs, we estimated the proportions of patients who are treated with bisphosphonates, treated with denosumab, or untreated, and the rates of SREs specific for each group. Lower rates of SREs were applied for the treated populations compared to the untreated population. Despite its strengths, there were some other limitations associated with our analysis. Latin American country-specific data were limited, both in terms of availability and quality. For some model inputs (i.e., treatment distribution and productivity losses), we relied on KOL feedback only. Treatment distribution for Mexico was assumed as the average of the other countries, given that country-specific data were unavailable. Finally, there was variability in the methodology used to cost the management of SREs between the limited sources available.

**Conclusion**

In the Latin American countries included in our analysis, the one-year burden of SREs in 2020 is approximately USD 1.4 billion, and the projected five-year burden is USD 6.9 billion. Despite recommendations for the use of BTA in patients with ST and bone metastasis and with MM and lytic bone lesions, a large proportion of patients who are at risk of experiencing...
SREs are not treated. Early detection of bone metastases and SREs and the use of the most effective preventative treatments are needed to decrease the clinical and economic burden of SREs in Latin America.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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Author contributions

All authors were involved in the conception and design of the study. AZ and DG were involved in the analysis of data and all authors contributed to the interpretation of data. All authors participated in the drafting of the paper and critical revisions for intellectual content. All authors approved the final version. All authors agree to be accountable for all aspects of the work.

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References

[1] Coleman R. Bisphosphonates: clinical experience. Oncologist. 2004;9(Suppl 4):14–27.
[2] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine combined with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513–1520.
[3] Scher HI, Morris MJ, Kelly WK, et al. Prostate cancer clinical trial end points: “RECiST”ing a step backwards. Clin Cancer Res. 2005;11(14):5223–5232.
[4] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502–1512.
[5] Hameed A, Brady JJ, Dowling P, et al. Bone disease in multiple myeloma: pathophysiology and management. Cancer Growth Metastasis. 2014;7:33–42.
[6] Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer. 2000;88(5):1082–1090.
[7] Silbermann R, Roodman G. Hematologic malignancies and bone. In: Rosen C, editor. Primer on the multiple myeloma-related complications. 8th ed. Ames (IA): Wiley-Blackwell; 2013.
[8] Fallowfield L, Cleeland C, Von Moos R. Pain progression and analgesic use after skeletal-related events in patients with solid tumors and bone metastases. Support Care Cancer 2016;24:1327–1337.
[9] Norgaard M, Jensen AO, Jacobsen JB, et al. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). J Urol. 2010;184(1):162–167.
[10] Yong M, Jensen AO, Jacobsen JB, et al. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999–2007). Breast Cancer Res Treat. 2011;129(2):495–503.
[11] Laubach J, Richardson P, Anderson K. Multiple myeloma. Annu Rev Med. 2011;62:249–264.
[12] Coleman R, Body JJ, Aapro M, et al. Bone health in cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2014;25(Suppl 3):iii124–iii137.
[13] Hagiwara M, Delea TE, Cong Z, et al. Utilization of intravenous bisphosphonates in patients with bone metastases secondary to breast, lung, or prostate cancer. Support Care Cancer. 2014;22(1):103–113.
[14] Rosen LS, Gordon D, Tchekmedyjan NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer. 2004;100(12):2613–2621.
[15] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, Double-Blind study. Lancet. 2011;377(9768):813–822.
[16] Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28(35):5132–5139.
[17] Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29(9):1125–1132.
[18] Al Farii H, Frazer A, Farahdel L, et al. Bisphosphonates versus denosumab for prevention of pathological fracture in advanced cancers with bone metastasis: a meta-analysis of randomized controlled trials. J Am Acad Orthop Surg Glob Res Rev. 2020;4(8):e2000045.
[19] Henry D, Vadhan-Raj S, Hirsh V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumours. Support Care Cancer. 2014;22(3):679–687.
[20] Delea T, McKiernan J, Brandman J, et al. Retrospective study of the effect of skeletal complications on total medical care costs in patients with bone metastases of breast cancer seen in typical clinical practice. J Support Oncol. 2006;4(7):341–347.
[21] Hoefeler H, Duran I, Hechmati G, et al. Health resource utilization associated with skeletal-related events in patients with bone metastases: results from a multinational retrospective – prospective observational study – a cohort from 4 European countries. J Bone Oncol. 2014;3(2):40–48.
[22] Hechmati G, Cure S, Gouepo A, et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. J Med Econ. 2013;16(5):691–700.
[23] Lothgren M, Ribniczec E, Schmidt L, et al. Cost per patient and potential budget implications of denosumab compared with zoledronic acid in adults with bone metastases from solid tumours and other skeletal-related events: a prospective cohort study from patients with solid tumors. Support Care Cancer. 2014;22(3):679–687.
who are at risk of skeletal-related events: an analysis for Austria, Sweden and Switzerland. Eur J Hosp Pharm. 2013;20(4):227–231.

[24] Bhowmik D, Hines DM, Intorcia M, et al. Economic burden of skeletal-related events in patients with multiple myeloma: analysis of US commercial claims database. J Med Econ. 2018;21(6):622–628.

[25] Biermann WA, Cantor RI, Fellin FM, et al. An evaluation of the potential cost reductions resulting from the use of clodronate in the treatment of metastatic carcinoma of the breast to bone. Bone. 1991;12(Suppl 1):S37–S42.

[26] Goodwin JA, Coleman EA, Sullivan E, et al. Personal financial effects of multiple myeloma and its treatment. Cancer Nurs. 2013;36(4):301–308.

[27] Broder MS, Gutierrez B, Cherepanov D, et al. Burden of skeletal-related events in prostate cancer: unmet need in pain improvement. Support Care Cancer. 2015;23(1):237–247.

[28] Barlev A, Song X, Ivanov B, et al. Payer costs for inpatient treatment of pathologic fracture, surgery to bone, and spinal cord compression among patients with multiple myeloma or bone metastasis secondary to prostate or breast cancer. J Manag Care Pharm. 2010;16(9):693–702.

[29] McDougall JA, Bansal A, Goulart BH, et al. The clinical and economic impacts of Skeletal-Related events among medicare enrollees with prostate metastatic to bone. Oncologist. 2016;21(3):320–326.

[30] Qian Y, Song X, Zhang K, et al. Short-term disability in solid tumor patients with bone metastases and skeletal-related events. J Med Econ. 2015;18(3):210–218.

[31] Schulman KL, Kohles J. Economic burden of metastatic bone disease in the U.S. Cancer. 2007;109(11):2334–2342.

[32] Felix J, Andreozzi V, Soares M, et al. Hospital resource utilization and treatment cost of skeletal-related events in patients with metastatic breast or prostate cancer: estimation for the Portuguese national health system. Value Health. 2011;14(4):499–505.

[33] Luftner D, Lorusso V, Duran I, et al. Health resource utilization associated with skeletal-related events in patients with advanced breast cancer: results from a prospective, multinational observational study. SpringerPlus. 2014;3:328.

[34] Pereira J, Body JJ, Gunther O, et al. Cost of skeletal complications from bone metastases in six European countries. J Med Econ. 2016;19(6):611–618.

[35] McGowan J, Sampson M, Salzwedel DM, et al. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40–46.

[36] Canadian Agency for Drugs and Technologies in Health (CADTH). Grey matters: a practical tool for searching health-related grey literature; 2018 [updated 2015]. Available from: https://www.cadth.ca/resources/finding-evidence/grey-matters

[37] Bank of America. Foreign exchange rates for U.S. Dollars; 2020. Available from: https://www.bankofamerica.com/foreign-exchange/exchange-rates.go

[38] Central Bank of Argentina. Central Bank of Argentina; 2020. Available from: http://www.bcra.gov.ar/

[39] Cristino J, Finek J, Maniadakis N, et al. The clinical and economic burden of skeletal related events in Austria, Czech Republic, Germany, Greece, Italy, Spain and Switzerland: a comparison between the use of denosumab and zoledronic acid in patients with prostate cancer and bone metastases. Value Health. 2015;18(7):A483.

[40] Institute for Health Metrics and Evaluation. GBD compare: University of Washington; 2017 [cited 2020 Feb]; Available from: https://vizhub.healthdata.org/gbd-compare/

[41] Cristino J, Finek J, Jandova P, et al. Cost-effectiveness of denosumab versus zoledronic acid for preventing skeletal-related events in the Czech Republic. J Med Econ. 2017;20(8):799–812.

[42] Stopeck A, Brufsky A, Kennedy L, et al. Cost-effectiveness of denosumab for the prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. J Med Econ. 2020;23(1):37–47.

[43] World Health Organization. Global Cancer Observatory (Globocan) [cited 2020 Feb 15]. Available from: https://gco.iarc.fr/today/home

[44] National Cancer Institute. Surveillance, epidemiology, and end results program [cited 2020 Feb 15]. Available from: https://seer.cancer.gov/

[45] The World Bank Group. DataBank; 2020. Available from: https://databank.worldbank.org/home.aspx

[46] Hungria VTM, Lee JH, Maialino A, et al. Survival differences in multiple myeloma in Latin America and Asia: a comparison involving 3664 patients from regional registries. Ann Hematol. 2019;98(4):941–949.

[47] Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018;19(3):370–381.

[48] Macherey S, Monsef I, Jahn F, et al. Bisphosphonates for advanced prostate cancer. Cochrane Database Syst Rev. 2017;12:CD006250.

[49] Mhashkar R, Kumar A, Miladinovic B, et al. Bisphosphonates in multiple myeloma: an updated network Meta-analysis. Cochrane Database Syst Rev. 2017;12:CD003188.

[50] O’Carrigan B, Wong MH, Willson ML, et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017;10:CD003474.

[51] Pérez M, García Perlaza J, Fletscher P, et al. Economic burden associated with Skeletal-Related events in patients with bone metastases in Colombia. Value Health. 2017;20(9):A423.

[52] University College London. CCEMG – EPPi-Centre Cost Converter v.1.4; 2020. Available from: https://eppii.ioe.ac.uk/costconversion/

[53] Tanaka S, Suri G, Arancibia A, et al. Impacto economico da adacao de denosumab em pacientes com metastases osseas ou mieloma multiplo sob a perspectiva do sistema de saude privado brasileiro. J Bras Econ Saude (Impr). 2020;12(1):16–22.

[54] IMSS. GRD – IMSS: 2018. Grupos Relacionados con el Diagnostico: Producto hospitalario. Direccion de Prestaciones Medicas; 2018.

[55] IMSS. ACUERDO ACDO. AS3.HCT.271119/329.P.DF; 2019.

[56] Instituto Mexicano del Seguro Social. ACUERDO ACDO. AS3.HCT.271119/329.P.DF; 2019.

[57] Instituto Mexicano del Seguro Social. GRD – IMSS: 2018. Grupos Relacionados con el Diagnostico: Producto hospitalario. Direccion de Prestaciones Medicas; 2018

[58] Body JJ, Pereira J, Sleeboom H, et al. Health resource utilization associated with skeletal-related events: results from a retrospective European study. Eur J Health Econ. 2016;17(6):711–721.

[59] Diel I, Anzorge S, Hohmann D, et al. Real-world use of denosumab and bisphosphonates in patients with solid tumours and bone metastases in Germany. Support Care Cancer. 2020;28(11):5223–5233.

[60] Alibhai SMH, Zukotynski K, Walker-Dilks C, et al. Bone health and bone-targeted therapies for prostate cancer: a programme in evidence-based care – cancer care Ontario clinical practice guideline. Clin Oncol. 2017;29(6):348–355.

[61] Haynes I, Woll PJ, Flinoi A, et al. Insights into the management of bone metastases in patients with lung cancer: a comprehensive European survey. Poster presented at: European Cancer Congress 2013 (ECCO-ESMO-ESTRO); 2013 Sep 27-Oct 1; Amsterdam, The Netherlands.

[62] Carter JA, Botteman MF. Health-economic review of zoledronic acid for the management of skeletal-related events in bone-metastatic prostate cancer. Expert Rev Pharmacoecon Outcomes Res. 2012;12(4):425–437.

[63] Liauw W, Segelov E, Lih A, et al. Off-trial evaluation of bisphosphonates in patients with metastatic breast cancer. BMC Cancer. 2005;5:89.
[65] Body JJ, Acklin YP, Gunther O, et al. Pathologic fracture and healthcare resource utilisation: a retrospective study in eight European countries. J Bone Oncol. 2016;5(4):185–193.

[66] von Moos R, Body JJ, Guenther O, et al. Healthcare-resource utilization associated with radiation to bone across eight European countries: results from a retrospective study. J Bone Oncol. 2018;10:49–56.

[67] Peters DH, Garg A, Bloom G, et al. Poverty and access to healthcare in developing countries. Ann N Y Acad Sci. 2008;1136:161–171.