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RESEARCH ARTICLE

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Socioeconomic and insurance-related disparities in disease-specific survival among patients with metastatic bone disease

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Abstract

Background: Approximately 5% of cancer patients in the United States presented with metastatic bone disease (MBD) at diagnosis. Current study explores the disparities in survival for patients with MBD.

Methods: Patients with the diagnosis of MBD at presentation for the five most common primary anatomical sites were extracted from Surveillance, Epidemiology, and End Results Census tract–level dataset (2010–2016). Kaplan–Meier and Cox Proportional Hazard models were used to evaluate survival, and prognostic factors for each cohort. Prognostic significance of socioeconomic status (SES) and insurance status were ascertained.

Results: The five most common anatomical-sites with MBD at presentation included "lung" (n = 59 739), "prostate" (n = 19 732), "breast" (n = 16 244), "renal and urothelium" (n = 7718) and "colon" (n= 3068). Lower SES was an independent risk factor for worse disease-specific survival (DSS) for patients with MBD originating from lung, prostate, breast and colon. Lack of insurance was an independent risk factor for worse DSS for MBD patients with primary tumors in lung and breast.

Conclusions: MBD patients from the five most common primary sites demonstrated SES and insurance-related disparities in disease-specific survival. This is the first and largest study to explore SES and insurance-related disparities among patients specifically afflicted with MBD. Our findings highlight vulnerability of patients with MBD across multiple primary sites to financial toxicity.

KEYWORDS
disparities, insurance, metastatic bone disease, socioeconomic, survival

Level of Evidence: Retrospective review of population-based data, Level of evidence 2.

1 | INTRODUCTION

More than 17 million people are currently living with cancer in the United States, and this number is predicted to increase to 22.2 million by 2030.[1] In 2020, the National Cancer Institute reported that the total cost of cancer care in the United States exceeded 208 million dollars.[2,3] Among all individuals with cancer, more than 5% will exhibit spread from the primary site to the skeletal system, referred to as metastatic bone disease (MBD).[4,5] The economic burden of MBD is disproportionately high, accounting for more than 20% of US cancer care expenditures.[4,6]

The National Institute of Minority Health and Health Disparities defines health disparities research as that which addresses health differences in socially disadvantaged populations related to specific outcomes, including: (1) higher incidence or prevalence; (2) earlier or higher mortality rate; (3) increased global burden of disease; (4) poorer health behaviors and clinical outcomes related to the previous outcomes; (5) worse outcomes on validated and specific patient reported outcome measures.[7] In the context of cancer, disparities in the incidence, prevalence, rate of screening, stage at initial presentation, morbidity, survival, and financial burden of disease have been reported for multiple primary malignanices.[1] We have recently highlighted disparities in incidence of MBD for the five most common primary sites.[8] In the present investigation, we were interested in assessing disparities in survival for patients with MBD, given that bone is one of the most common sites of metastatic disease[5,8,9] and also that metastatic disease is the most common malignant process affecting the skeletal system [4,10]

Patients with MBD have advanced systemic disease and face unique treatment challenges.[6,11,12] MBD is associated with significant morbidity and functional compromise. Historically, patient with MBD at initial presentation had reduced life expectancy with treatment efforts primarily focused on pain control and palliation. Fortunately, with recent advances in treatment, the life expectancy for patients with MBD has improved considerably.[11,12] Thus, while patients with MBD are now living longer, they face new challenges related to optimizing their quality of life.[6] Specifically, sarcopenia, cachexia, and pain associated with MBD have the potential to shift a patients primary concern from longevity to more nuanced anxieties pertaining to simple activities of daily living,[6,13,14] kinesiophobia, and low pain self-efficacy.[15]

Taken together, MBD is a major factor influencing the quality of life in patients with cancer. However, the disparities for disease-specific survival (DSS) among patients with MBD have not been comprehensively reported in the literature.[16–20] Considering the disproportionately higher costs associated with the care of patients afflicted with MBD as well as the observed improvement in life expectancy, we examined the relationship between the socioeconomic and insurance-related disparities and DSS of patients with MBD from the five most common sites.[8]

2 | METHODS

Case information was extracted from the NCI's Surveillance Epidemiology End Results (SEER) program as outlined in our recent publication.[1,8] SEER currently collects the data from 22 registries covering approximately 48% of the US population.[1] The presence of MBD at the time of diagnosis became available only after 2010. SEER does not capture the development of metastasis among patients who initially presented with non-metastatic disease, thus underestimating true burden of MBD. We utilized the "Incidence-SEER 18 Regs (Excl AK) Custom Data (with additional treatment fields), Nov 2018 Sub (2000–2016) < Vintage 2016 Pops by Tract 2000/2010 Mixed Geographies>" to extract cases with MBD at presentation from 2010 to 2016. Information regarding patients' age, sex, race/ethnicity recode (Non-Hispanic White [NHW], Non-Hispanic Black [NHB], Non-Hispanic American Indian Alaskan Native [NHAIAN], Non-Hispanic Asian Pacific Islander [NHAPI], and Hispanics), primary site, grade, size of the primary tumor, histologic subtypes, cause of death, year of diagnosis, surgical and radiation treatment of the primary tumor site, chemotherapy, surgery other site, and survival time until death or loss to follow-up was extracted.

For our analysis, we grouped primary malignancies originating from "trachea and bronchus" with primary malignancies originating from "lung and pleura." Primary urothelial malignancies ("urinary collecting system including bladder") were grouped with those originating from the "kidney and renal pelvis."

Information regarding socioeconomic status (SES) and insurance was extracted using the custom SEER census tract level and rurality database from 2000 to 2016.[21] Insurance was evaluated as a potential disparity affecting outcomes in patients with MBD. Patients with insurance at time of presentation were categorized as "insured," while we grouped noninsured patients with Medicaid patients, as patients presenting without insurance to a healthcare facility are enrolled in Medicaid.[22] Medicaid patients were combined with uninsured patients based upon previously presented evidence in the literature.[22,23] Uninsured patients are retroactively enrolled in Medicaid and have been coded as having "Medicaid" in the national databases.[22,23] Alternate analyses were conducted modeling different combinations of insurance categories such as combining Medicare, Medicaid and no insurance into one group; and conclusions were the same.

Small area SES was analyzed as a composite index calculated by SEER using the method described by Yost et al.[24] Census tract-level SES indicator variables of median household income, median house value, median rent, percentage of the population below 150% of the poverty line, an education index, percentage of the population with working class occupations, and percentage of population older than 16 years in the workforce without a job were utilized.[24] The data are presented as quintiles, with Group 1 representing the lowest SES and Group 5 representing the highest SES. The SES data was collected at the time of initial presentation. Patients with missing data were excluded from each respective univariable and multivariable analysis.

Age was converted to a categorical variable (0–14, 15–39, 40–64, ≥65) for the purpose of analysis. We chose this stratification to align with adolescent and young adult population demographics being defined at 15–39.[25,26] Staging categories of local, regional and distant disease were used according to the SEER staging system.[27] Only cases with a staging category of "distant" were included in the current investigation. Size of primary tumor was also converted to a categorical variable (<5 cm, ≥5 cm) for the purpose of analysis. In the SEER dataset, "Surgery other site" denotes a surgical procedure performed at a site other than the primary malignancy and/or lymph node, but lacks further detail on anatomic location. This variable was included in the analysis as surgeries for MBD would be coded under this variable.

Statistical analyses were performed using SPSS Statistical package version 27.0 (SPSS Inc.). The log-rank test was utilized for categorical values to gauge the effects of demographic, clinical, pathological, treatment and socioeconomic variables. Variables achieving statistical significance on univariable analyses ($p < 0.05$) were included in multivariable analyses. A Cox proportional hazards (Cox P-H) model. was performed for identification of independent prognostic factors with the proportional hazard ratio of death from a particular malignancy.

3 | IRB APPROVAL

The study was deemed exempt from institutional review board approval.

4 | RESULTS

Demographic and clinical characteristics stratified by primary sites are presented in Table 1. The five most common sites with MBD were lung ($n = 59\,739$), prostate ($n = 19\,732$), breast ($n = 16\,244$), renal ($n = 7\,718$) and colon ($n = 3068$). Details of histopathological diagnoses for each of the primary sites are summarized in Table S1.

The most common age group for patients presenting with MBD was ">65 years" for all primary sites except breast. The most common age group for patients with primary breast malignancy and MBD was "40–64 years" (51.1%) followed by ">65 years" (42.8%). MBD was more common in males for all primary sites except breast (females: 98.7%) (Table 1). NHW was the most common race/ethnicity for patients with MBD across all primary sites. Most of the MBD patients had insurance and were almost equally distributed among different SES quintiles (Table 1). MBD patients without insurance ranged from 23.7% (breast) to 16.7% (prostate) of the respective cohort. SES quintile distribution ranged from 22.5% (Group 2, renal) to 17.5% (Group 5, lung).

The most common grade for primary malignancies originating from lung (62.5%) and prostate (89.4%) was "poorly differentiated." However, for MBD patients with a primary breast (47.6%) or colon (54.3%) malignancy, "moderately differentiated" grade was more common. Renal (46.6%) primary malignancies with MBD were more likely to present with an "undifferentiated" grade. A majority of the patients presenting with MBD did not undergo surgical resection of the "primary tumor" or "surgery other site." When performed, surgery for "other site" was most common for primaries originating from renal cancer (10.6%). Of note, a majority of patients with MBD did not have brain, lung or liver metastasis, with the only exception being MBD patients with primary colon disease, of which 70.4% had concurrent liver metastasis.

The lowest 1- and 2-year DSS was observed for MBD patients with primary lung disease (10% and 5%, respectively); followed by colon (15% and 8%), renal (17% and 12%), prostate (55% and 42%) and breast (56% and 43%), respectively. The results of univariable analysis are summarized in Table 2. Statistically significant prognostic factors in the univariable analysis were analyzed in a Cox P-H model.

On multivariable analysis (Table 3), for MBD patients with lung cancer primary, younger age, male sex, NHAPI, size <5 cm, surgical resection of the primary tumor, radiotherapy, chemotherapy and insurance (Figure 2A) were independent protective factors of improved DSS. Lower SES (Figure 1A), "undifferentiated" grade, and NHW and NHB race/ethnicity (Figure 2B) were independent risk factors of worse DSS.

For patients with prostate cancer presenting with MBD, "moderately" differentiated grade and smaller size of the primary tumor were independent protective factors of improved DSS. SES Group 2 was an independent risk factor of poor DSS (Figure 1B).

Younger age, "well-differentiated" and "moderately" differentiated grade, radiotherapy, chemotherapy, and insurance (Figure 2C) were independent protective factors of improved DSS for breast cancer patients with MBD. Race/ethnicity groups of NHW, NHB (Figure 2D), and SES groups 1 and 2 (Figure 1C) were risk factors of poor DSS in the breast cancer cohort.

For patients with renal primary, age group "40–64 years," surgical resection of the primary tumor, "surgery other site" (Figure 2E), radiotherapy and chemotherapy were statistically significance as prognostic factors on multivariable analysis. "Undifferentiated" grade was a risk factor of worse DSS. Of note, neither insurance nor SES groups were statistically associated with DSS in the Cox P-H model for renal primary.

For patients with colon cancer presenting with MBD, age group "40–64 years," "well differentiated" grade, size <5 cm, surgical resection of the primary tumor, radiotherapy, and chemotherapy were found to be associated with improved DSS. The lowest SES group (Figure 1D) was an independent risk factor for worse DSS.

5 | DISCUSSION

Certain aspects of SES and insurance-related disparities in DSS have been reported for patients with lung, prostate, breast, renal and colon primary cancer sites.[28–36] However, the SES and insurance-related disparity profile for patients with MBD arising from these primary malignancies have not been reported.[16–20] MBD patients presents

TABLE 1 Demographics and clinical characteristics metastatic bone disease stratified by primary anatomical sites

	Lung		Prostate		Breast		Renal		Colon	
	n	Valid 100% of total	*n*	Valid 100% of total	*n*	Valid 100% of total	*n*	Valid 100% of total	*n*	Valid 100% of total
Total patients	59 739	100	19 732	100	16 244	100	7718	100	3068	100
Age										
00–14 years	4	0	0	0	0	0	17	0.2	0	0
15–39 years	429	0.7	10	0.1	994	6.1	126	1.6	108	3.5
40–64 years	21 686	36.3	5505	27.9	8295	51.1	3078	39.9	1405	45.8
≥65 years	37 620	63	14 217	72.1	6955	42.8	4497	58.3	1555	50.7
Sex										
Male	34 073	57	19 732	100	16 033	98.7	5387	69.8	1865	60.8
Female	25 666	43			211	1.3	2331	30.2	1203	39.2
Race/ethnicity										
NH White	44 619	74.8	12 793	65.2	10 913	67.4	5545	71.9	1956	63.9
NH Black	6650	11.1	3397	17.3	2447	15.1	756	9.8	469	15.3
NHAPI	4398	7.4	1119	5.7	1067	6.6	426	5.5	243	7.9
NHAIAN	204	0.3	110	0.6	63	0.4	59	0.8	21	0.7
Hispanic	3801	6.4	2213	11.3	1707	10.5	927	12	373	12.2
Grade										
Well differentitated	888	4.7	121	1	1169	9.8	87	2.7	102	5.7
Moderate	4481	23.8	1026	8.6	5683	47.6	433	13.3	966	54.3
Poorly	11 759	62.5	10 673	89.4	5008	42	1223	37.4	604	34
Undifferentiated	1680	8.9	114	1	67	0.6	1521	46.6	102	5.7
B/T/NK cells	10	0.1			2	0	3	0.1	4	0.2
Size										
<5 cm	27 237	61.4	556	71.8	8188	66.4	1685	30.6	766	52.3
≥5 cm	17 146	38.6	218	28.2	4142	33.6	3822	69.4	700	47.7
Size										
Surgery	872	1.5	1899	9.7	3799	23.8	2784	36.2	715	23.5
No surgery	58 709	98.5	17 723	90.3	12 162	76.2	4897	63.8	2328	76.5

TABLE 1 (Continued)

	Lung		Prostate		Breast		Renal		Colon	
	n	Valid 100% of total	*n*	Valid 100% of total	*n*	Valid 100% of total	*n*	Valid 100% of total	*n*	Valid 100% of total
Surgery other site										
Other site surgery	2744	4.6	684	3.5	745	4.6	819	10.6	242	7.9
LN surgery	284	0.5	119	0.6	62	0.4	54	0.7	16	0.5
No surgery other site	56 610	94.9	18 858	95.9	15 396	95	6831	88.7	2799	91.6
Radiation therapy										
Radiotherapy	27 965	97.1	12	6.6	5470	96.2	3406	98.2	893	97.6
None/unknown	832	2.9	28	15.4	215	3.8	64	1.8	22	2.4
Chemotherapy										
Chemotherapy	31 719	53.1	2544	12.9	7914	48.7	3778	49	1704	55.5
None/Unknown	28 020	46.9	17 188	87.1	8330	51.3	3940	51	1364	44.5
Insurance										
Insurance	48 125	82.2	15 871	83.3	12 102	76.3	6158	81.5	2301	76.9
No Insurance/medicaid	10 419	17.8	3184	16.7	3758	23.7	1394	18.5	693	23.1
SES										
Group 1	11 477	20.2	3807	20.5	3005	19.5	1350	18.5	625	21.3
Group 2	12 035	21.2	3614	19.5	3067	19.9	1645	22.5	615	21
Group 3	11 934	21.1	3712	20	3048	19.7	1510	20.7	562	19.2
Group 4	11 288	19.9	3813	20.5	3247	21	1469	20.1	572	19.5
Group 5	9947	17.5	3633	19.6	3071	19.9	1336	18.3	555	18.9
Brain metastasis										
Brain mets	12 921	22.4	217	1.2	1138	7.3	627	8.4	146	5
No brain mets	44 863	77.6	18 613	98.8	14 484	92.7	6848	91.6	2780	95
Lung metastasis										
Lung mets	16 274	28.5	1433	7.6	4211	26.9	3244	43.4	1270	43
No lung mets	40 893	71.5	17 358	92.4	11 423	73.1	4224	56.6	1684	57
Liver metastasis										
Liver mets	18 081	31.2	752	4	3731	23.6	1660	22.1	2120	70.4
No liver mets	39 936	68.8	18 203	96	12 049	76.4	5857	77.9	892	29.6

Abbreviations: NHAIAN, Non-Hispanic American Indian Alaskan Native; NHAPI, Non-Hispanic Asian Pacific Islander; SES, socioeconomic status.

TABLE 2 Disease-specific survival according to demographic and clinical characteristics

	Lung			Prostate			Breast			Renal			Colon		
	1 year	2 years	*p* value	1 year	2 years	*p* value	1 year	2 years	*p* value	1 year	2 years	*p* value	1 year	2 years	*p* value
Total patients	10	5	n/a	55	42	n/a	56	43	n/a	17	12	n/a	15	8	
Age															
00–14 years	43	0								83	83				
15–39 years	29	19		34	20		72	58		23	16		24	17	
40–64 years	12	7		65	50		61	47		23	16		19	9	
≥ 65 years	8	4	<0.001	52	39	<0.001	47	35	<0.001	13	8	<0.001	11	6	<0.001
Sex															
Male	8	4		55	42		51	41		18	12		15	7	
Female	12	7	<0.001	n/a	n/a	n/a	56	43	0.355	16	11	0.023	16	9	0.915
Race/ethnicity															
NH White	8	4		55	41		56	43		17	11		14	7	
NH Black	8	4		55	41		47	34		17	11		15	6	
NHAPI	22	13		65	52		60	46		20	14		23	13	
NHAIAN	10	7		54	41		69	56		9	7		8	0	
Hispanic	14	8	<0.001	55	41	<0.001	60	49	<0.001	20	14	0.004	18	10	0.002
Grade															
Well differentiated	19	12		80	66		74	59		25	22		21	10	
Moderate	16	9		76	65		65	51		41	35		24	12	
Poorly	9	5		63	48		51	37		23	16		10	5	
Undifferentiated	4	2	<0.001	36	27	<0.001	28	21	<0.001	15	9	<0.001	9	3	<0.001
Size															
<5 cm	12	7		67	53		62	48		21	16		22	11	
≥5 cm	7	4		44	30	<0.001	55	41	<0.001	20	13	0.399	16	10	<0.001
Surgery															
Surgery	25	18		59	46		73	60		28	21		25	15	
No surgery	9	5	<0.001	55	41	<0.001	50	37	<0.001	11	6	<0.001	12	5	<0.001

TABLE 2 (Continued)

	Lung			Prostate			Breast			Renal			Colon		
	1 year	2 years	*p* value	1 year	2 years	*p* value	1 year	2 years	*p* value	1 year	2 years	*p* value	1 year	2 years	*p* value
Surgery other site															
Other site surgery	13	7		55	38		63	50		34	25		23	17	
LN surgery	13	9		49	27		73	61		7	7		5	0	
No surgery other site	9	5	<0.001	56	42	0.147	55	42	<0.001	15	10	<0.001	15	7	<0.001
Radiation therapy															
Radiotherapy	11	6		56	43		61	47		21	14		20	11	
None/unknown	3	2	<0.001	33	25	<0.001	28	18	<0.001	3	0	<0.001	9	9	<0.001
Chemotherapy															
Chemotherapy	15	8		59	41		63	50		22	14		22	11	
None/unknown	3	2	<0.001	55	42	<0.001	49	36	<0.001	12	9	<0.001	7	4	<0.001
Insurance															
Insurance	10	6		56	42		58	45		18	12		15	8	
No Insurance/medicaid	8	5	<0.001	53	39	0.011	50	36	<0.001	16	9	0.009	15	7	0.242
SES															
Group 1	7	3		52	39		50	37		15	10		13	5	
Group 2	7	4		52	40		52	39		17	12		14	8	
Group 3	9	5		55	42		54	41		17	12		16	8	
Group 4	11	7		57	43		59	45		17	11		18	11	
Group 5	14	8	<0.001	60	45	<0.001	63	50	<0.001	20	13	<0.001	17	10	<0.001

Note: Disease-specific survival according to demographic and clinical characteristics of the metastatic bone disease stratified by primary sites.

Abbreviations: NHAIAN, Non-Hispanic American Indian Alaskan Native; NHAPI, Non-Hispanic Asian Pacific Islander; SES, socioeconomic status.

Survival data is presented as percentage of the total for respective categories.

Lung:

Age: $p < 0.001$ is true only for "15–39 years versus 40–64 years," "15–39 years versus >65 years," and "40–64 years versus >65 years"; $p = 0.584$ for "0–14 years versus 15–39 years"; $p = 0.116$ for "0–14 years versus 40–64 years"; $p = 0.046$ for "0–14 years versus >65 years."

Race/ethnicity: $p < 0.001$ is true only for "NHW versus NHAPI," "NHW versus Hispanic," "NHB versus NHAPI," "NHB versus Hispanic," and "NHAIAN versus NHAPI"; $p = 0.592$ for "NHW versus NHB"; $p = 0.381$ for "NHW versus NHAIAN"; $p = 0.331$ for "NHB versus NHAIAN" and $p = 0.149$ for "NHAIAN versus Hispanic."

Grade: $p < 0.001$ is true only for "Well differentiated versus Poorly," "Well differentiated versus Undifferentiated," "Moderate versus Poorly," and "Moderate versus Undifferentiated"; $p = 0.002$ for "Well differentiated versus Moderate"; and $p = 0.007$ for "Poorly versus Undifferentiated."

Surgery other site: $p < 0.001$ is true only for "Other site surgery versus No surgery other site"; $p = 0.877$ for "other site surgery versus LN surgery"; $p = 0.007$ for "LN surgery versus No surgery other site."

SES: $p < 0.001$ is true for all comparisons between all groups.

Prostate:

Age: $p < 0.001$ is true only for "40–64 years versus >65 years"; $p = 0.009$ for "15–39 years versus 40–64 years"; and $p = 0.210$ for "15–39 years versus >65 years."

Race/ethnicity: $p < 0.001$ is true only for "NHW versus NHAPI," "NHB versus NHAPI" and "NHAPI versus Hispanic"; $p = 0.204$ for "NHW versus NHB"; $p = 0.955$ for "NHW versus NHAIAN"; $p = 0.093$ for "NHW versus Hispanics"; $p = 0.867$ NHB versus NHAIAN; $p = 0.571$ NHB versus Hispanic; $p = 0.037$ "NHAPI versus NHAIAN" and $p = 0.717$ for "NHAIAN versus Hispanic."

Grade: $p < 0.001$ is true only for 'Well differentiated versus Undifferentiated', 'Moderate versus Poorly', 'Moderate versus Undifferentiated' and 'Poorly versus Undifferentiated'; $p = 0.436$ for 'Well differentiated versus Moderate'; $p = 0.066$ for 'Well differentiated versus Poorly'

Surgery other site: $p = 0.147$ only for "Other site surgery versus No surgery other site"; $p = 0.697$ for "Other site surgery versus LN surgery"; and $p = 0.408$ for "LN surgery versus No Surgery other site."

SES: $p < 0.001$ is true only for "Group 1 versus Group 5" and "Group 2 versus Group 5"; $p = 0.424$ for "Group 1 versus Group 2"; $p = 0.008$ for "Group 1 versus Group 3"; $p = 0.002$ for "Group 1 versus Group 4"; $p = 0.071$ for "Group 2 versus Group 3"; $p = 0.02$ for "Group 2 versus Group 4"; $p = 0.64$ for "Group 3 versus Group 4"; $p = 0.002$ for "Group 3 versus Group 5," and $p = 0.009$ for "Group 4 versus Group 5."

Breast:

Age: $p < 0.001$ is true for all comparisons between all groups.

Race/ethnicity: $p < 0.001$ is true only for "NHW versus NHB," "NHW versus Hispanics," "NHB versus NHAPI," "NHB versus NHAIAN," and "NHB versus Hispanics"; $p = 0.068$ for "NHW versus NHAPI"; $p = 0.025$ for "NHW versus NHAIAN"; $p = 0.067$ for "NHAPI versus NHAIAN"; $p = 0.417$ for "NHAPI versus Hispanic," and $p = 0.097$ for "NHAIAN versus Hispanics."

Grade: $p < 0.001$ is true for all comparisons for all groups.

Surgery other site: $p < 0.001$ only for "Other site surgery versus No surgery other site"; $p = 0.752$ for "Other site surgery versus LN Surgery," and $p = 0.102$ for "LN Surgery versus No surgery other site."

SES: $p < 0.001$ is true only for "Group 1 versus Group 3," "Group 1 versus Group 4," "Group 1 versus Group 5," "Group 2 versus Group 4," "Group 2 versus Group 5," "Group 3 versus Group 4," and "Group 3 versus Group 5"; $p = 0.05$ for "Group 1 versus Group 2"; $p = 0.041$ for "Group 2 versus Group 3," and $p = 0.032$ for "Group 4 versus Group 5."

Renal and Urothelium:

Age: $p < 0.001$ is true for all comparisons except: $p = 0.378$ for "15–39 years versus 40–64 years."

Race/ethnicity: $p = 0.004$ is true only for "NHW versus Hispanic"; $p = 0.528$ for "NHW versus NHB"; $p = 0.032$ for "NHW versus NHAPI"; $p = 0.413$ for "NHW versus NHAIAN"; $p = 0.034$ for "NHB versus NHAPI"; $p = 0.541$ for "NHB versus NHAIAN"; $p = 0.009$ for "NHB versus Hispanic"; $p = 0.123$ for "NHAPI versus NHAIAN"; $p = 0.958$ for "NHAPI versus Hispanics," and $p = 0.102$ for "NHAIAN versus Hispanics."

Grade: $p < 0.001$ is true only for "Moderate versus Poorly," "Moderate versus Undifferentiated," and "Poorly versus Undifferentiated"; $p = 0.002$ for "Well differentiated versus Moderate"; $p = 0.589$ for "Well differentiated versus Poorly," and $p = 0.039$ for "Well differentiated versus Undifferentiated."

Surgery other site: $p < 0.001$ is true for all comparisons except: $p = 0.155$ for "LN surgery versus No surgery other site."

SES: $p < 0.001$ is true only for "Group 1 versus Group 5" and "Group 2 versus Group 5"; $p = 0.098$ for "Group 1 versus Group 2"; $p = 0.017$ for "Group 1 versus Group 3"; $p = 0.002$ for "Group 1 versus Group 4"; $p = 0.403$ for "Group 2 versus Group 3"; $p = 0.11$ for "Group 2 versus Group 4"; $p = 0.441$ for "Group 3 versus Group 4"; $p = 0.007$ for "Group 3 versus Group 5" and $p = 0.052$ for "Group 4 versus Group 5."

Colon:

Age: $p < 0.001$ is true for all comparisons except: $p = 0.094$ for "15–39 years versus 40–64 years."

Race/ethnicity: $p = 0.002$ is true only for "NHW versus NHAPI"; $p = 0.546$ for "NHW versus NHB"; $p = 0.765$ for "NHW versus NHAIAN"; $p = 0.04$ for "NHW versus Hispanic"; $p = 0.018$ for "NHB versus NHAPI"; $p = 0.679$ for "NHB versus NHAIAN"; $p = 0.159$ for "NHB versus Hispanic"; $p = 0.25$ for "NHAPI versus NHAIAN"; $p = 0.229$ for "NHAPI versus Hispanic"; and $p = 0.48$ for "NHAIAN versus Hispanic."

Grade: $p < 0.001$ is true only for "Well differentiated versus Poorly," "Moderate versus Poorly," "Moderate versus Undifferentiated"; $p = 0.479$ for "Well differentiated versus Moderate"; $p = 0.005$ for "Well differentiated versus Undifferentiated" and $p = 0.879$ for "Poorly versus Undifferentiated."

Surgery other site: $p < 0.001$ is true only for "Other site surgery versus No surgery other site"; $p = 0.225$ for "Other site surgery versus LN surgery"; and $p = 0.836$ for "LN Surgery versus No surgery other site."

SES: $p < 0.001$ is true only for "Group 1 versus Group 4" and "Group 1 versus Group 5"; $p = 0.01$ for "Group 2 versus Group 1"; $p = 0.002$ for "Group 1 versus Group 3"; $p = 0.724$ for "Group 2 versus Group 3"; $p = 416$ for "Group 2 versus Group 4"; $p = 0.116$ for "Group 2 versus Group 5"; $p = 0.656$ for "Group 3 versus Group 4"; $p = 0.221$ for "Group 3 versus Group 5" and $p = 0.469$ for "Group 4 versus Group 5."

TABLE 3 Cox Proportional hazards model for risk of death for MBD stratified by primary sites

Multivariable analysis	Lung			Prostate			Breast			Renal			Colon		
	n	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value
Age															
00–14 years										1	0	0.883			
15–39 years	71	0.513	<0.001				295	0.494	<0.001	29	0.815	0.356	15	0.679	0.253
40–64 years	2921	0.899	<0.001	55	0.642	0.189	1945	0.663	<0.001	627	0.764	<0.001	192	0.711	0.019
≥65 years	4241	Reference group		73	Reference group		1166	Reference group		639	Reference group		119	Reference group	
Sex															
Male	4126	0.824	<0.001							370	1.017	0.817			
Female	3107	Reference group								926	Reference group				
Race/ethnicity															
NH White	5329	1.307	<0.001	75	2.28	0.12	2305	1.201	0.033	966	1.151	0.185	208	1.138	0.52
NH Black	844	1.154	0.025	21	1.96	0.266	497	1.503	<0.001	101	1.212	0.206	42	0.899	0.668
NHAPI	553	0.861	0.037	14	2.526	0.14	229	1.122	0.363	69	1.249	0.201	24	1.641	0.112
NHAIAN	29	1.128	0.568				14	0.722	0.4	7	1.245	0.608	1	0.007	0.969
Hispanic	478	Reference group		18	Reference group		361	Reference group		153	Reference group		51	Reference group	
Grade															
Well differentiated	321	0.693	<0.001	1	0	0.979	322	0.26	<0.001	27	0.602	0.021	15	0.349	0.011
Moderate	1802	0.753	<0.001	16	0.054	0.017	1584	0.346	<0.001	215	0.431	<0.001	185	0.714	0.164
Poorly	4572	0.94	<0.001	107	0.388	0.161	1485	0.634	0.105	484	0.724	<0.001	100	1.229	0.421
Undifferentiated	538	Reference group		4	Reference group		15	Reference group		570	Reference group		26	Reference group	
Size															
<5 cm	4008	0.801	<0.001	91	0.355	0.001	2243	0.857	0.002				192	0.739	0.022
≥5 cm	3225	Reference group		37	Reference group		1163	Reference group					134	Reference group	

(Continues)

TABLE 3 (Continued)

Multivariable analysis	Lung			Prostate			Breast			Renal			Colon		
	n	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value	*n*	Hazard ratio	*p* value
Surgery															
Surgery	235	0.586	<0.001	24	0.649	0.312	1432	0.46	<0.001	930	0.411	<0.001	137	0.714	0.016
No surgery	6998	Reference group		104	Reference group		1974	Reference group		366	Reference group		189	Reference group	
Surgery other site															
Other site surgery	337	0.953	0.44				212	0.82	0.055	190	0.729	0.001	43	0.837	0.396
LN surgery	16	1.413	0.198				9	0.85	0.747	8	1.095	0.827	5	1.701	0.312
No surgery other site	6880	Reference group					3185	Reference group		1098	Reference group		278	Reference group	
Radiation therapy															
Radiotherapy	7051	0.781	0.002	126	1.011	0.992	3300	0.571	<0.001	1278	0.448	0.002	323	10.634	0.023
None/unknown	182	Reference group		2	Reference group		106	Reference group		18	Reference group		3	Reference group	
Chemotherapy															
Chemotherapy	4552	0.391	<0.001	26	0.771	0.62	1926	0.851	0.002	786	0.626	<0.001	252	0.276	<0.001
None/unknown	2681	Reference group		102	Reference group		1480	Reference group		510	Reference group		74	Reference group	
Insurance															
Insurance	6032	0.902	0.005	108	1.982	0.22	2587	0.799	<0.001	1097	0.841	0.065			
No Insurance/ medicaid	1201	Reference group		20	Reference group		819	Reference group		199	Reference group				
SES															
Group 1	1434	1.108	0.021	30	2.278	0.146	628	1.293	0.002	195	1.119	0.336	66	1.664	0.019
Group 2	1541	1.119	0.007	20	3.466	0.028	693	1.325	<0.001	300	1.192	0.082	67	0.707	0.121
Group 3	1497	1.117	0.008	22	1.021	0.968	680	1.15	0.076	260	0.945	0.59	76	1.372	0.12
Group 4	1442	1.017	0.684	24	2.198	0.139	739	0.927	0.345	280	1.036	0.728	53	1.403	0.131
Group 5	1319	Reference group		32	Reference group		666	Reference group		261	Reference group		64	Reference group	

Abbreviations: MBD, metastatic bone disease; NHAIAN, Non-Hispanic American Indian Alaskan Native; NHAPI, Non-Hispanic Asian Pacific Islander; SES, socioeconomic status.

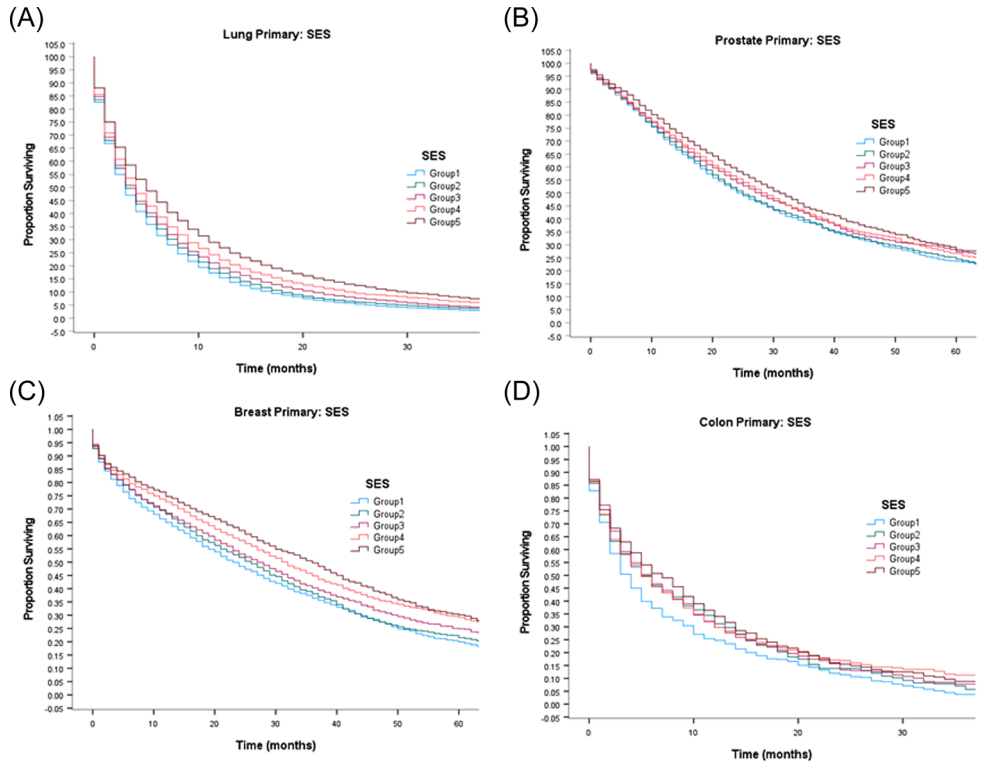

FIGURE 1 Kaplan–Meier curves representing disease-specific survival among MBD patients for different SES groups for tumors originating from: (A) lung, (B) prostate, (C) breast, (D) colon. MBD, metastatic bone disease; SES, socioeconomic status

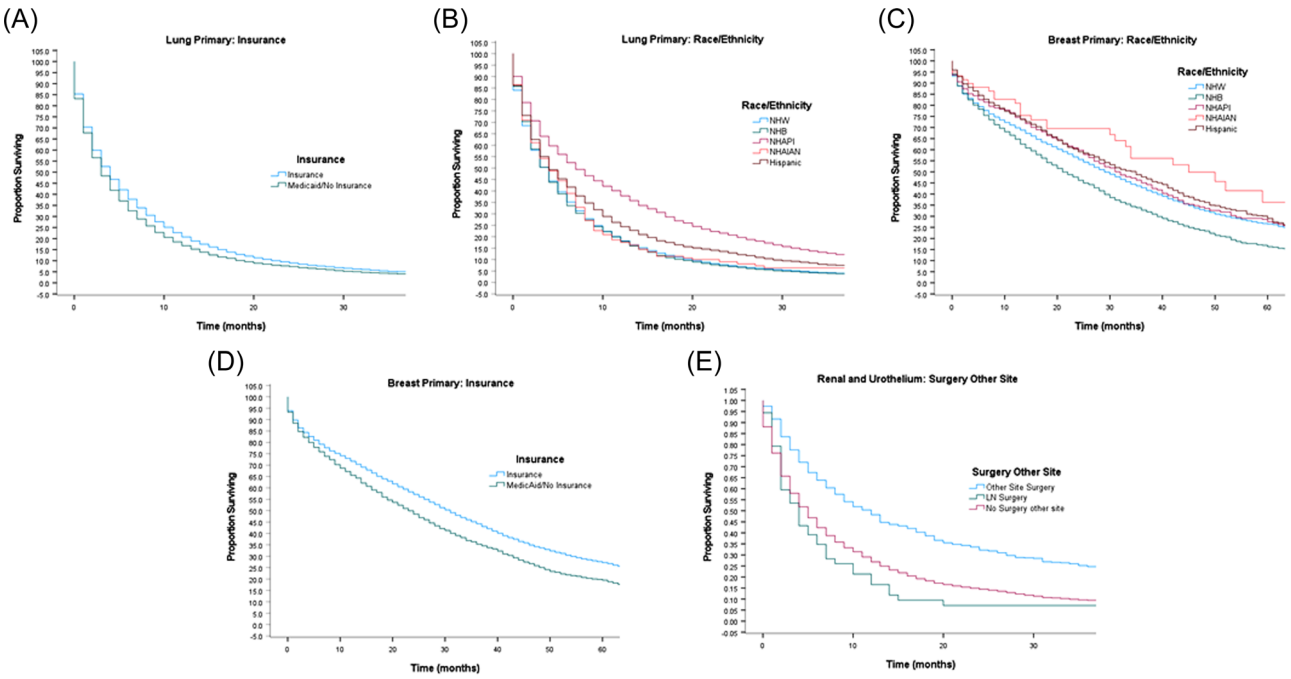

FIGURE 2 Kaplan–Meier curves representing disease-specific survival among MBD patients for: (A) Insurance status in patients with primary tumor in lung, (B) race/ethnicity in patients with primary tumor in lung, (C) race/ethnicity in patients with primary tumor in breast, (D) insurance status in patients with primary tumor in breast, (E) surgery other than primary site in patients with primary tumor in renal and urothelium. MBD, metastatic bone disease

unique challenges. Bone metastases are painful and if left untreated can result in a pathological fracture. Pathological fractures are potentially devastating consequences of MBD, and can negatively impact patient's quality of life by limiting their mobility and necessitating surgery in many cases. Repair of pathologic fractures in turn is associated with a number of potentially life-threatening complications such as nonunion, malunion, deep venous thrombosis, pulmonary embolism, hospital acquired pneumonia, hypercalcemia of malignancy, and other morbidities.[37,38]

Numerous studies have attempted to classify the risk of impending fracture for metastatic bone lesions.[39,40] Ultimately, when the clinical evidence portends a risk for pathologic fracture, prophylactic stabilization versus reconstruction is typically planned to mitigate the physical and psychosocial sequalae of a realized pathological fracture.[41–44] Additionally, radiation is usually administered pre- or postoperatively to the involved area.[43,44] Patients with MBD thus present with a distinct and high-risk profile and for that reason we chose to focus the current investigation on the SES and insurance-related disparities in this cohort.

SES related disparities in disease-specific survival of patients with MBD was seen in four of the five most common primary anatomic sites. The only primary anatomic site not showing any SES-related disparity in DSS was "renal and urothelium." Renal and urothelial cancer patients presenting with MBD have 1- and 2-year DSS of 17% and 12%, respectively. SES was significant prognostic factor on univariable analysis, however, lost its significance on multivariable analysis. Given the available data in the SEER database, it is out of the scope of current investigation to speculate the reason behind this finding.

Another interesting finding of our investigation was the lack of synchronous metastases to other sites in patients with MBD. Recent laboratory evidence suggests that metastases present in bone can actually potentiate tumor cells metastasizing to other organs.[9,45,46] In the current investigation, a majority of patients presenting with MBD did not have synchronous metastases to other common sites i.e., brain, lung, and liver (Table 1), suggesting that bone metastases are early events in cancer progression. For the four most common sites contributing to bone metastasis, synchronous metastases were found in a minority of patients (Table 1). The only exception to this observation was metastases originating from a primary colon site, with more than 70% of these patients exhibiting synchronous liver metastases. This high incidence of liver metastasis in malignancies originating from the gastrointestinal tract is expected due to the unique anatomical features of splanchnic circulation. Taken together with the recent basic science evidence,[9,45,46] these findings call for future clinical/translational investigations focused on elucidating the role of bone serving as a potentiating site for other organ metastases. If confirmed, addressing disparities in MBD by SES would become even more important for achieving equity in outcomes.

Patients with MBD secondary to primary lung malignancy had the worst 1- and 2-year DSS (10% and 5%, respectively; Table 2). When compared to reported DSS for patients with "distant" stage (5-year DSS 4.7%),[47] the DSS for MBD was worse (5-year DSS 2.0%, data not shown). This finding supports the idea that lung cancer patients with MBD represent a subgroup that is at increased risk of mortality compared to patients with metastasis to other organs. SES disparities in the survival for lung cancer have been widely reported in the literature.[47–50] Our findings are consistent with previously reported SES disparities in DSS, even for terminal stage of disease. Lack of insurance was also an independent predictor of a poor DSS in the current analysis. There is evidence to suggest a positive impact of smoking cessation on prognosis for patients with metastatic nonsmall cell lung cancer.[51] One of the limitations of our analysis is the absence of tobacco use data in the SEER database.

Prostate cancer patients with MBD had the second-best prognosis among the five most common primary sites (Table 2). Siegel et al.[52] recently reported a 5-year survival rate of 32.3% for metastatic prostate cancer. We found a somewhat lower 5-year DSS for patients with MBD in the setting of a primary prostate cancer (20%, data not shown). In general, the evidence regarding SES disparities and survival for patients with prostate cancer has been inconsistent in the literature.[53] Klein and Knesebeck[53] performed a systemic review of 46 articles, reporting significant association between low SES and worse survival among prostate cancer patients. Our analysis revealed SES Group 2 (2nd lowest SES group) to be an independent risk factor of poor DSS for MBD patients with prostate cancer.

Breast cancer patients with MBD had the best DSS among the five most common primary sites (Table 2). According to the American Society of Clinical Oncology, the estimated 5-year survival for patients with metastatic breast cancer is 28%.[54] In our cohort, 5-year DSS was 17% (data not shown) for breast cancer patients with MBD, although we did not exclude patients with synchronous metastasis to other sites. In isolation, breast cancer patients with bone-only metastasis have better overall survival and DSS compared to patients with nonskeletal metastatic disease such as brain and lung.[55] SES disparities have been widely reported to influence survival among patients with breast cancer.[56,57] Current investigation confirms these SES disparities in patients with MBD. SES disparities in survival among patients with breast cancer exist despite "safety net" programs such as Medicare and Medicaid.[56,57] Having health insurance was found to be an independent predictor of improved survival on multivariable Cox regression in this study.

Renal and urothelial carcinoma patients presenting with MBD have the third worst DSS (17%: 1 year and 12%: 2 years; Table 2) among the five most common primary sites. The American Cancer Society reports a 5-year survival rate of 13% for kidney cancer with distant stage.[58] In our analysis, renal and urothelial primary cancer patients with MBD had a 5-year DSS of 4% (data not shown). Our analysis did not reveal any SES or insurance disparities for renal and urothelial patients with MBD. These findings were consistent with a recent report from the National Cancer Database did not show disparities with respect to median income.[59] In our analysis, a total of 43.4% of this group of patients with MBD had synchronous lung metastasis. Lung has been suggested as the most common site for renal-cell carcinoma metastasis, as the renal vein drains directly into

the inferior vena cava.[60] A unique finding in our analysis was identifying the prognostic significance of "surgery other site" in DSS for the renal and urothelial carcinoma MBD group. In the SEER dataset, "surgery other site" denotes a surgical procedure performed at a site other than the primary malignancy and/or lymph node, but lacks further detail on anatomic location. Given that renal-cell metastases to bone are notoriously destructive, often necessitating a bone stabilizing procedure to mitigate pain and improve function,[61,62] and further considering that all patients in our selection had MBD, it is reasonable to assume that some fraction of "surgery other site" was referring to a bony stabilizing procedure. However, SEER lacks any further detail about "surgery other site." To our knowledge, there has been no suggestion of a prognostic significance of bone stabilizing procedures in the literature.[63] Bone stabilization for metastatic lesions has so far been regarded as a palliative procedure.[6] This finding calls for an in-depth analysis of a large dataset with more granularity about bone stabilizing procedures. Also, renal cell carcinoma has a variety of histologic subtypes with varying prognosis. A detailed analysis of MBD in different histologic subtypes is beyond the scope of current investigation.

Colon was the fifth most common primary site contributing to MBD in the current analysis. Although some prior studies have shown thyroid to be the fifth most common primary site leading to MBD,[10] another analysis of SEER data reported a similar finding to the current study.[5] Socioeconomic disparities have long been implicated in incidence and mortality associated with colon cancer.[64–67] The current analysis highlights lowest SES as being an independent predictor of poor prognosis. Insurance status, however, was not a predictor of DSS in colon primaries presenting with MBD.

Our study has limitations associated with large database analysis. Information regarding clinical course, radiological exam, serology, and other medical comorbidities is not included in the SEER database. Information regarding specific chemotherapy regimen is missing and data in the cohort was presented as a binary variable: "yes versus none/unknown," making it difficult to draw definitive conclusions. Details for "surgery other site" is also missing in the SEER data. Another limitation is the lack of individual-level SES data. The only SES measure included as part of the SEER database is area-level SES. Although details of staging data and radiographic images is lacking in the SEER database, others have used SEER bone metastasis data as a gold standard to assess the validity of Medicare claims data.[68] Patients who develop bone metastasis while being on treatment and after enrollment in the SEER program are not captured in the SEER coding of MBD.

This is the first and the largest study to explore the SES and insurance related disparities among patients specifically afflicted with MBD from the five most common primary sites utilizing population-based data in the United States. We have recently demonstrated wide-spread socioeconomic disparities in the incidence of MBD.[8] Taken together, the findings should prompt a higher degree of suspicion and screening among at risk strata, to facilitate earlier diagnosis and subsequent earlier access to care. The findings are also important for public health policy. Resource allocation from available funds towards early detection and treatment for patients in the lower socioeconomic strata and lacking health insurance is required to address these disparities.

AUTHOR CONTRIBUTIONS

R. Lor Randall, Steven W. Thorpe, Brad H. Pollock, and Barton L. Wise: conception and editing. **Amy Cizik and Betty Ferrell**: data extraction. **Lauren N. Zeitlinger, Edmond F. O' Donnell, and Janai R. Carr-Ascher**: analysis. **Muhammad Umar Jawad**: manuscript preparation.

CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

Available at https://seer.cancer.gov/data-software/

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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