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Mortality associated with osteoporosis and pathological fractures in the United States (1999–2020): a multiple-cause-of-death study

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Abstract

Background Osteoporosis with pathological fractures is a significant public health issue, contributing to morbidity, disability, diminished quality of life, and increased mortality. Understanding mortality trends related to this condition is crucial for developing effective interventions to reduce mortality and improve healthcare outcomes. This study aimed to analyze trends and causes of death associated with osteoporosis and pathological fractures in the United States using a multi-cause approach.

Methods Annual death and age-standardized mortality rate (ASMR) data from 1999 to 2020 were obtained from the Centers for Disease Control and Prevention (CDC) mortality database. Death certificates listing ICD-10 M82 (osteoporosis with pathological fracture) as an underlying or related cause of death were analyzed. Epidemiological data were analyzed, and the ASMR data were calculated for each year, and trends were assessed using the Cochran-Armitage trend test.

Results From 1999 to 2020, there were 40,441 deaths related to osteoporosis with pathological fractures in the United States, with a female-to-male ratio of 5.6:1. Among these, 12,820 deaths (31.7%) listed osteoporosis with pathological fractures as the underlying cause of death (UCD), yielding a female-to-male ASMR ratio of approximately 5.0-7.7:1. When classified as a non-UCD, the ASMR ratio was approximately 4.8–6.2:1. At the same time, we found that the total number of deaths classified as UCD and multiple causes of death (MCD), but the trend ratio of the two groups in different years did not change statistically significant ($P > 0.05$), and the ASMR of both groups showed a downward trend. The UCD-to-MCD ratio increased between 1999 and 2007, then decreased from 2007 to 2020. As MCD, the number of female deaths was more than that of male, and both showed a decreasing trend, but there was no statistical significance in the change of trend ratio in different years ($P > 0.05$). Deaths were predominantly concentrated in individuals over 75 years of age, with those over 84 years being the most affected. The number

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of deaths in different age groups showed a decreasing trend, and the change of trend ratio in different years was statistically significant ($P < 0.05$). White individuals had the highest number of deaths. The leading causes of death were heart diseases, chronic lower respiratory diseases, and alzheimer's disease. In addition, the number of deaths of patients with prostate cancer and breast cancer showed a significant downward trend, and the change of trend ratio between the two groups in different years was statistically significant ($P < 0.05$).

Conclusions Although mortality from osteoporosis with pathological fractures is decreasing, anti-osteoporosis therapy remains essential for elderly patients. Healthcare providers should remain vigilant for potential complications, including malignant neoplasms, and ensure timely diagnosis and treatment to further reduce mortality in this population.

Keywords Osteoporosis, Pathological fracture, Mortality, Malignant tumor

Background

Osteoporosis is a systemic bone disease characterized by low bone mass, deterioration of bone tissue microstructure, increased bone fragility, and a heightened susceptibility to fractures [1]. It is a serious, chronic, progressive, and clinically asymptomatic condition, and it is the most common metabolic bone disease [2]. Osteoporosis is more prevalent in the elderly, typically affecting men over 65 years of age and women over 55 years of age [3, 4]. The overall prevalence of osteoporosis is approximately 20% [5], with a global prevalence of about 12% in men and 23% in women [6, 7].

Starting at the age of 50, one in three women and one in five men will experience an osteoporotic fracture [4]. In 2000, there were an estimated 9 million new osteoporotic fractures worldwide, including 1.7 million forearm fractures, 1.4 million clinical vertebral fractures, and 1.6 million hip fractures [8]. Fragility fractures of the spine and hip are associated with an increased risk of mortality [9]. Studies have shown that the one-year mortality rate for older adults with osteoporotic fractures is approximately 15% for women and 22% for men. By 2009, the annual mortality rate had decreased to 11.2% for women and 18% for men, and by 2010, it had further declined to 2.8% for women and 3.6% for men [10]. However, the number of deaths related to osteoporosis and pathological fractures, as well as the trend in age-standardized mortality rates (ASMR) in the United States, remain unclear.

Cancer and cardiovascular disease are the leading causes of death among the elderly, and when osteoporosis is combined with pathological fractures, the risk of death increases [11]. However, the underlying cause of death in cases of osteoporosis with pathological fractures and the sequence of events leading to death remain unclear. Additionally, bone metastasis occurs in 65–90% of prostate cancer cases and 65–75% of breast cancer cases [12, 13]. Bone involvement is less common in other malignancies, ranging from approximately 10% in colorectal cancer to 17–64% in lung cancer [12, 13]. Bone metastasis is a major risk factor for bone loss and fractures [14]. This is attributable both to the direct effects of cancer cells on bone and the detrimental effects of cancer-specific therapies on bone cells [15]. Bone is also the most common site of metastasis, leading to bone destruction and the formation of pathological fractures [16]. In recent years, the mortality trends for osteoporosis combined with pathological fractures in the context of breast and prostate cancer remain unclear, warranting further investigation.

Therefore, this study aimed to describe the mortality associated with osteoporosis and pathological fractures, as well as to identify the leading causes of death, using multiple cause-of-death data from Centers for Disease Control and Prevention (CDC) death certificates spanning the past 22 years.

Methods

Using a multi-cause approach, we extracted annual mortality data (1999–2020) from the CDC mortality database, selecting all deaths associated with osteoporosis and pathological fractures (International Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] category M80: osteoporosis with pathological fracture). These cases were identified when osteoporosis with pathological fracture was listed as a cause of death on any line or in any part of the International Medical Certificate of Cause of Death (the medical certificate section of the death certificate) [17]. The underlying cause (Part I of the medical certificate section) and complications or contributing causes (Part II of the medical certificate section) were collectively designated as related (non-underlying) causes of death.

According to the ICD-10, osteoporosis with pathological fractures as a cause of death includes the following subcategory codes: M80.0 (postmenopausal osteoporosis with pathological fracture), M80.1 (postoophorectomy osteoporosis with pathological fracture), M80.2 (osteoporosis of disuse with pathological fracture), M80.3 (post-surgical malabsorption osteoporosis with pathological fracture), M80.4 (drug-induced osteoporosis with pathological fracture), M80.5 (idiopathic osteoporosis with pathological fracture), M80.8 (other osteoporosis with

pathological fracture), and M80.9 (unspecified osteoporosis with pathological fracture). Additional comorbidities considered include subcategory codes C50 (malignant neoplasm of the breast) and C61 (malignant neoplasm of the prostate).

We analyzed mortality, proportions, and historical trends to examine the distribution of the following variables: sex, age at death (categorized as <65 years, 65–74 years, 75–84 years, and >84 years), race, year of death, underlying cause of death, total contribution from each cause of death, and deaths from combined malignancies.

To identify relevant causes listed on the death certificate as contributing to death, we compiled a comprehensive list of commonly associated and frequently mentioned causes. The number of causes of death was categorized according to the range of ICD-10 classifications (subcategories, categories, blocks, and sections). We exported all causes of death into a table and filtered them by "subcategories, categories, blocks, and chapters" to determine their inclusion as causes of death. Deaths resulting from osteoporosis and pathological fractures were not counted in the total number of causes of death. If two or more causes listed in the medical certificate section fell within the same category, only one was recorded according to the ICD-10 category code. This approach prevented the duplication of causes, as presented in the summary table.

We calculated annual deaths from osteoporosis with pathological fractures and ASMR per 100,000 population. Mortality for the entire study period (1999–2020) was determined based on the number of deaths identified as the underlying or related cause and the total number of cited cases.

Data analysis was conducted using SPSS 26.0 (IBM, Armonk, New York, USA), and graphical representations were created using Graphpad Prism 8.0. The Cochran-Armitage trend test was used to assess trends across different years. A p-value of <0.05 was considered statistically significant, and all tests were conducted in a two-sided manner.

Results

In the United States, 6,746,356,647 deaths were recorded between 1999 and 2020, of which 40,441 were related to osteoporosis with pathological fractures. Among these, 34,334 (84.9%) were women and 6,107 (15.1%) were men, resulting in a female-to-male ratio of approximately 5.6:1 (Table 1). When classified as the underlying cause of death (UCD), there were 12,820 deaths (31.7%), with a female-to-male ASMR ratio (per 100,000 population) of approximately 5.0-7.7:1 (Table 1). When classified as a non-UCD, the number of deaths was 27,621 (68.3%), with the ASMR (per 100,000 population) for women and men being approximately 4.8–6.2:1 (Table 1). Additionally, we

Table 1 Number of osteoporosis with pathological fractures-related deatls in US from 1999 to 2020 stratified by year

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	All
All osteoporosis with pathological fracture-related deaths,no.	2362	2400	2432	2511	2372	2275	2330	2215	2203	2110	1839	1783	1805	1591	1451	1340	1375	1269	1238	1208	1190	1142	40441
Osteoporosis with pathological fracture listed as the UCD	694	735	731	790	779	721	759	722	759	725	620	555	599	524	450	425	465	407	365	363	339	293	12820
Men, no.	93	122	105	115	106	100	124	111	104	103	81	82	86	70	66	49	64	52	56	50	50	43	1832
Women, no.	601	613	626	675	673	621	635	611	655	622	539	473	513	454	384	376	401	355	309	313	289	250	10988
Ratio of women to men	6.5	5	6	5.9	6.3	6.2	5.1	5.5	6.3	6	6.7	5.8	6	6.2	5.8	7.7	6.3	6.8	5.5	6.3	5.8	5.8	6
Osteoporosis with pathological fracture listed as the NUCD	1668	1655	1701	1721	1593	1554	1571	1493	1444	1385	1212	1228	1206	1141	1001	915	910	862	873	845	851	849	27621
Men, no.	269	260	260	269	254	224	235	234	229	211	169	188	188	246	154	131	156	131	132	125	132	135	4275
Women, no.	1399	1395	1441	1452	1339	1330	1336	1259	1215	1174	1043	1040	1018	895	847	784	754	731	741	720	719	714	23346
Ratio of women to men	5.2	5.4	5.5	5.4	5.3	5.9	5.7	5.4	5.3	5.6	6.2	5.5	5.4	3.6	5.5	6	4.8	5.6	5.6	5.8	5.4	5.3	5.5
Age, no.																							
<65Years	66	55	70	69	60	64	66	49	55	59	40	49	39	44	28	40	24	43	38	32	28	39	1057
65–74 Years	197	178	172	154	159	161	153	126	128	123	115	93	110	94	90	81	86	73	73	79	88	86	2619
75–84 Years	691	739	734	773	703	658	661	630	601	548	452	456	426	363	346	272	289	241	256	239	258	235	10571
>84Years	1408	1428	1456	1515	1450	1392	1450	1410	1419	1380	1232	1185	1230	1090	987	948	976	912	871	858	816	782	26194

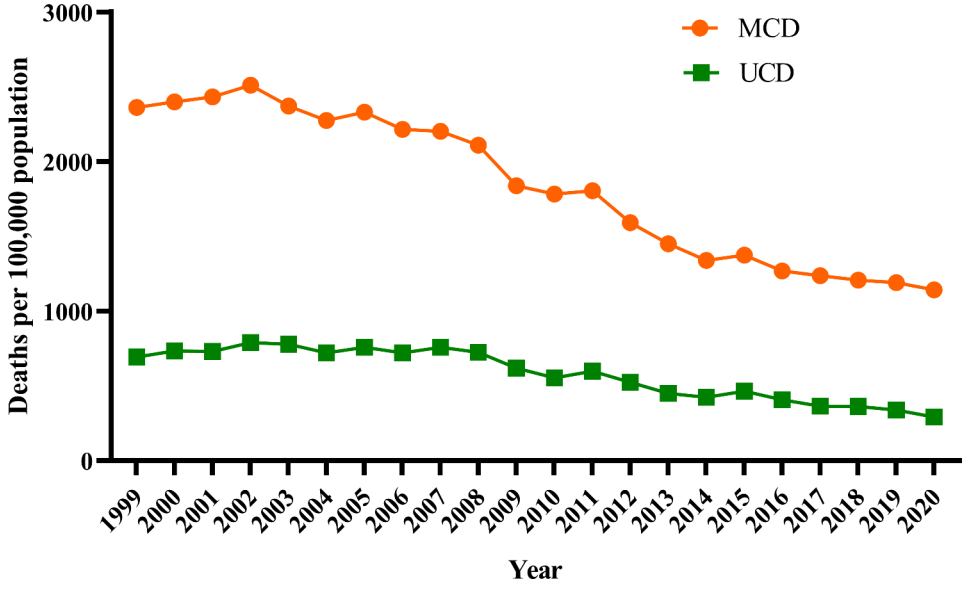

Fig. 1 Trends in the overall number of UCD and MCD deaths

Table 2 The U/M ratio from 1999 to 2020

Years	UCD			MCD			U/M
	No.	Rate.	95%CI	No.	Rate.	95%CI	%
1999	694	0.254	0.235–0.273	2362	0.871	0.836–0.907	29.4
2000	735	0.263	0.244–0.282	2400	0.866	0.832–0.901	30.6
2001	731	0.262	0.243–0.281	2432	0.861	0.827–0.896	30.1
2002	790	0.274	0.255–0.293	2511	0.882	0.847–0.917	31.5
2003	779	0.268	0.249–0.287	2372	0.828	0.794–0.861	32.8
2004	721	0.244	0.226–0.262	2275	0.78	0.748–0.812	31.7
2005	759	0.254	0.236–0.272	2330	0.778	0.746–0.81	32.6
2006	722	0.229	0.212–0.246	2215	0.72	0.69–0.75	32.6
2007	759	0.236	0.219–0.253	2203	0.692	0.663–0.721	34.5
2008	725	0.214	0.198–0.23	2110	0.649	0.621–0.677	34.4
2009	620	0.183	0.169–0.198	1839	0.555	0.53–0.581	33.7
2010	555	0.165	0.151–0.179	1783	0.527	0.502–0.552	31.1
2011	599	0.172	0.158–0.186	1805	0.517	0.493–0.541	33.2
2012	524	0.146	0.134–0.159	1591	0.443	0.421–0.465	32.9
2013	450	0.126	0.114–0.138	1451	0.396	0.375–0.417	31.0
2014	425	0.109	0.098–0.12	1340	0.357	0.338–0.376	31.7
2015	465	0.123	0.112–0.135	1375	0.354	0.335–0.373	33.8
2016	407	0.1	0.09–0.11	1269	0.327	0.308–0.345	32.1
2017	365	0.09	0.08–0.099	1238	0.308	0.29–0.325	29.5
2018	363	0.083	0.074–0.092	1208	0.303	0.286–0.321	30.0
2019	339	0.08	0.071–0.089	1190	0.293	0.276–0.309	28.5
2020	293	0.066	0.058–0.074	1142	0.273	0.257–0.289	25.7

observed a downward trend in the total number of deaths classified as UCD and multiple causes of death (MCD). However, there was no statistically significant change in the trend ratio between the two groups across different years ($p>0.05$) (Fig. 1). The ASMR for both groups also showed a downward trend. The ratio of UCD to MCD exhibited an increasing trend from 1999 to 2007, followed by a decreasing trend from 2007 to 2020 (Table 2).

When osteoporosis combined with pathological fracture was considered as a MCD, the number of deaths was higher in females than in males, with both showing a decreasing trend. This decline was more pronounced in females; however, the trend ratio between the two groups across different years was not statistically significant ($p>0.05$) (Fig. 2). In terms of mortality, the ASMR was significantly higher in women than in men, and both

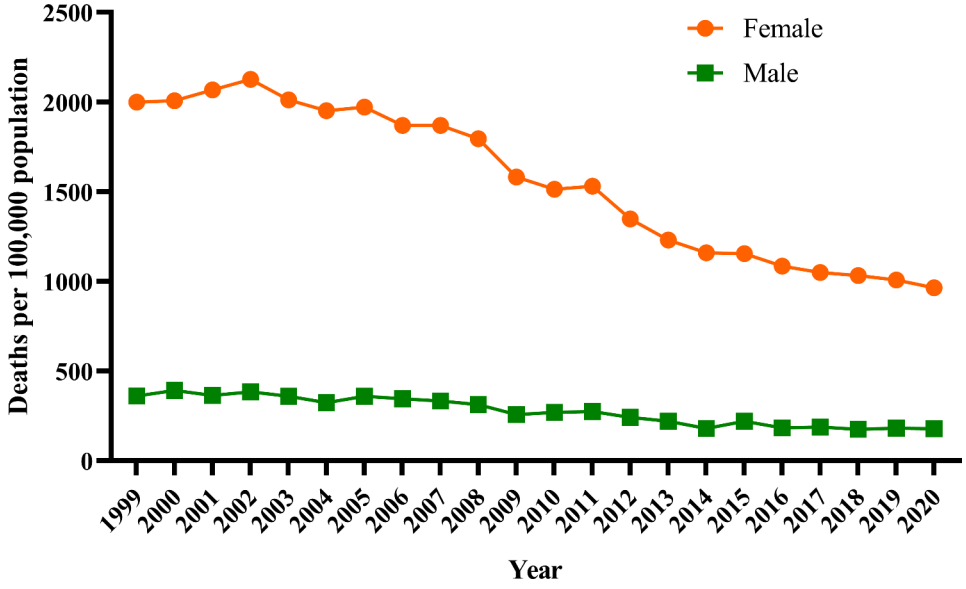

Fig. 2 Deaths by gender in the US from 1999 to 2020

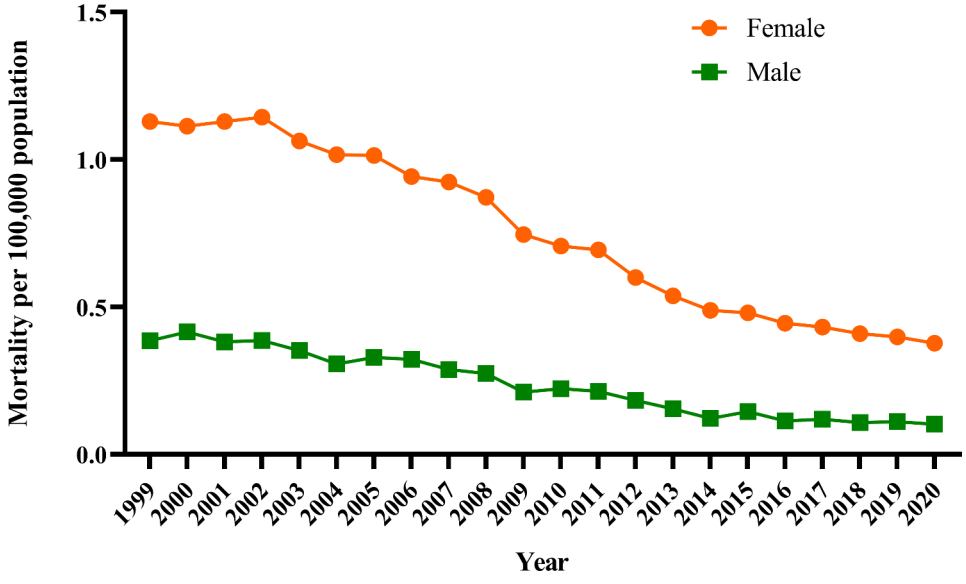

Fig. 3 ASMR by gender in the US from 1999 to 2020

sexes exhibited a downward trend, and this decline was more pronounced in women than in men (Fig. 3).

Regarding the number of deaths by age group, the majority of deaths occurred in patients over 75 years of age, with those over 84 years of age being the most affected (Table 1). Across all age groups, there was a downward trend in the number of deaths, with the trend ratio showing statistical significance over different years ($p<0.05$). The decline was observed year by year, and the older the age group, the more rapid the decrease (Fig. 4). In terms of race, the highest number of deaths occurred among White individuals, accounting for 39,090 deaths (96.7% of the total), This was followed by Asian or Pacific Islanders with 624 deaths (1.5%), Black or African Americans with 587 deaths (1.5%), and American Indian or Alaska Native individuals with 140 deaths (0.3%).

The UCD over the 22-year study period, ranked in descending order by the total number of mentions, are presented in Table 3. Diseases of the heart were the leading cause of death, followed by chronic lower respiratory diseases and alzheimer's disease.

Our study also found that between 1999 and 2020, when osteoporosis combined with pathological fracture was associated with malignant tumors as an MCD, the number of deaths in patients with prostate cancer and breast cancer was 329 and 813, respectively. The trend

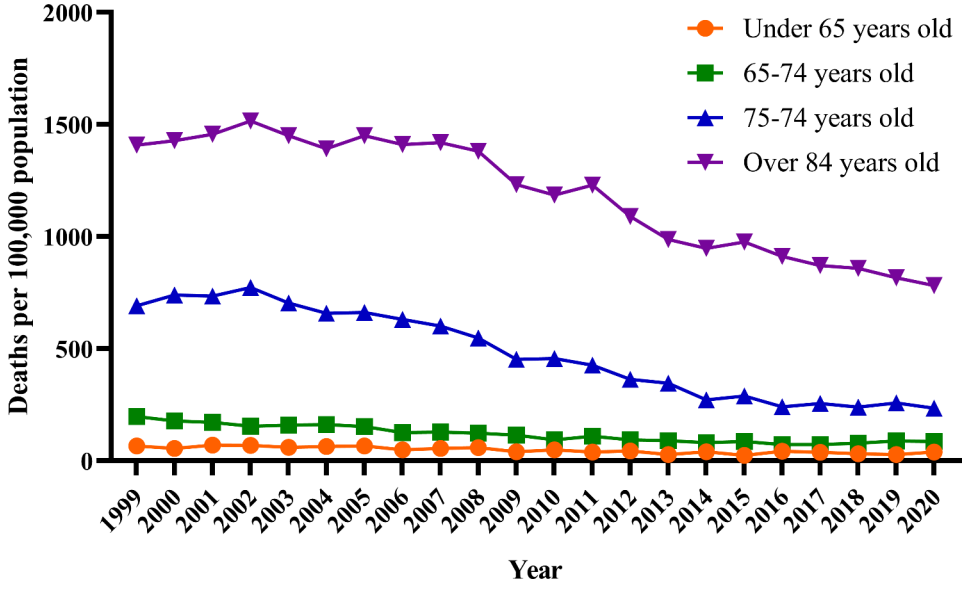

Fig. 4 The number of deaths in different age groups

ratio between these two groups across different years was statistically significant ($p<0.05$). However, the overall trend showed a decline, with the downward trend being more pronounced when prostate cancer was involved (Fig. 5).

Discussion

The results of this study show that from 1999 to 2020, the number of deaths from osteoporosis combined with pathological fractures was consistently higher in women than in men, with a mortality ratio of approximately 5.5:1. This higher number of deaths among women is associated with their higher morbidity rates. Generally, the incidence of fractures in women is nearly double that of men, with approximately 75% of such cases occurring in women [18]. Men have a lower risk of osteoporosis and fragility fractures than women, due to factors such as smaller bone diameters, lower peak bone mass, the bone resorption processes associated with menopause, and a higher risk of falls in women [19]. In the United States, 2 million osteoporotic fractures occur annually (71% in women and 29% in men) [20]. Our study also found that the ASMR was consistently higher in women than in men. However, previous studies have shown that men experience more osteoporosis-related complications and have higher mortality rates after osteoporotic fractures than women [21–23]. For instance, a 10-year study in Australia reported that the mortality rate after low-grade trauma fractures was 48% for women and 57% for men [24]. The reasons for the higher mortality rate in men are not entirely clear, but a higher risk of infection among males may be a contributing factor [25]. This discrepancy with our findings suggests the need for further investigation. Additionally, our study observed a downward trend in the annual mortality rate among elderly individuals with osteoporosis and pathological fractures starting in 1999 for both women and men [26]. This is generally consistent with our results, which showed a declining trend in ASMR in both sexes.

When osteoporosis with pathological fracture was considered either as an UCD or MCD, the number of deaths showed a decreasing trend. Moreover, the ratio of UCD to MCD also decline in the later stages, which may be attributed to the early diagnosis of osteoporosis through bone density screening and the timely treatment provided by clinicians [19]. Furthermore, the incidence of vertebral fractures in women begins to increase around the age of 60 and accelerates significantly after the age of 80. The incidence of hip fractures in women rises sharply after the age of 70 and peaks after the age of 80 [4]. For men, a Norwegian study reported that the incidence of hip fractures was 0.49 per 1000 person-years in men aged 60 and 12.3 per 1000 person-years in men aged 85 [27]. This indicates that osteoporosis and pathological fractures begin to rise sharply after the age of 70 and reach a peak after the age of 80. The spike in morbidity is likely closely related to the number of deaths, which, according to our findings, are predominantly concentrated in patients over 75 years of age, with those over 84 years of age being the most affected. Concurrently, we observed a downward trend in the number of deaths across all age groups, which may be linked to early diagnosis and the use of anti-osteoporosis medications [23, 28]. In our study, the highest number of deaths by race occurred among White individuals, which aligns with previous studies indicating the incidence of osteoporosis is approximately 50%

Table 3 Ranking of underlying causes of death in osteoporosis with pathological fracture mentioned from 1999 to 2020

Associated causes of death (ICD-10 chapters)	*n*
#Diseases of heart (I00-I09,I11,I13,I20-I51)	7294
#Chronic lower respiratory diseases (J40-J47)	3790
#Alzheimer disease (G30)	2443
#Malignant neoplasms (C00-C97)	2095
#Cerebrovascular diseases (I60-I69)	1356
#Accidents (unintentional injuries) (V01-X59,Y85-Y86)	1103
#Essential hypertension and hypertensive renal disease (I10,I12,I15)	516
#Diabetes mellitus (E10-E14)	507
#Parkinson disease (G20-G21)	387
#Pneumonitis due to solids and liquids (J69)	364
#Nephritis, nephrotic syndrome and nephrosis (N00-N07,N17-N19,N25-N27)	263
#Septicemia (A40-A41)	200
#Nutritional deficiencies (E40-E64)	193
#In situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (D00-D48)	189
#Atherosclerosis (I70)	163
#Chronic liver disease and cirrhosis (K70,K73-K74)	121
#Influenza and pneumonia (J09-J18)	114
#Enterocolitis due to Clostridium difficile (A04.7)	92
#Peptic ulcer (K25-K28)	73
#Anemias (D50-D64)	68
#Aortic aneurysm and dissection (I71)	58
#Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	50
#Complications of medical and surgical care (Y40-Y84,Y88)	48
#Hernia (K40-K46)	48
#COVID-19 (U07.1)	44
#Cholelithiasis and other disorders of gallbladder (K80-K82)	30
#Viral hepatitis (B15-B19)	25
#Tuberculosis (A16-A19)	13
#Pneumoconioses and chemical effects (J60-J66,J68,U07.0)	12

among White individuals, compared to 38% and 39% among Hispanics and African Americans, respectively. A prospective study of 159,579 women aged 50 to 79 years found that White individuals (2%) and Native Americans (2%) had the highest annualized fracture rates, followed by Hispanics (1.3%), Asians (1.2%), and African Americans (0.9%) [29, 30]. The incidence of osteoporosis with pathological fractures was highest among White women (140.7 per 100,000), followed by Asian women (85.4 per 100,000), African American women (57.3 per 100,000), and Hispanic women (49.7 per 100,000) [31]. This corresponds to the higher number of deaths observed among White individuals in our study.

Osteoporosis with pathological fractures is closely associated with increased mortality, particularly in the period following the fracture event [32]. Osteoporotic fractures, especially hip fractures, are often precipitated by falls, leading to a high risk of complications and rapid health deterioration. In fact, a significant proportion (53.8%) of early deaths (within 30 days) following a hip fracture are attributed to accidents involving injury, which are identified as the UCD—these are events that trigger a cascade of morbid events directly leading to death. This underlying cause of death remains prominent in the months following the fracture, accounting for about a quarter of all deaths within a year after the incident. In the later stages, circulatory diseases (particularly cardiovascular diseases) became the leading cause of death, followed by tumors, respiratory diseases, mental and behavioral disorders, and diseases of the nervous system and sensory organs [33]. A Swedish study corroborates these findings, identifying cardiovascular disease, cancer, and pneumonia as the leading causes of death [34]. Consistent with previous studies, our study found that the leading cause of death was heart disease. However, our findings differed slightly

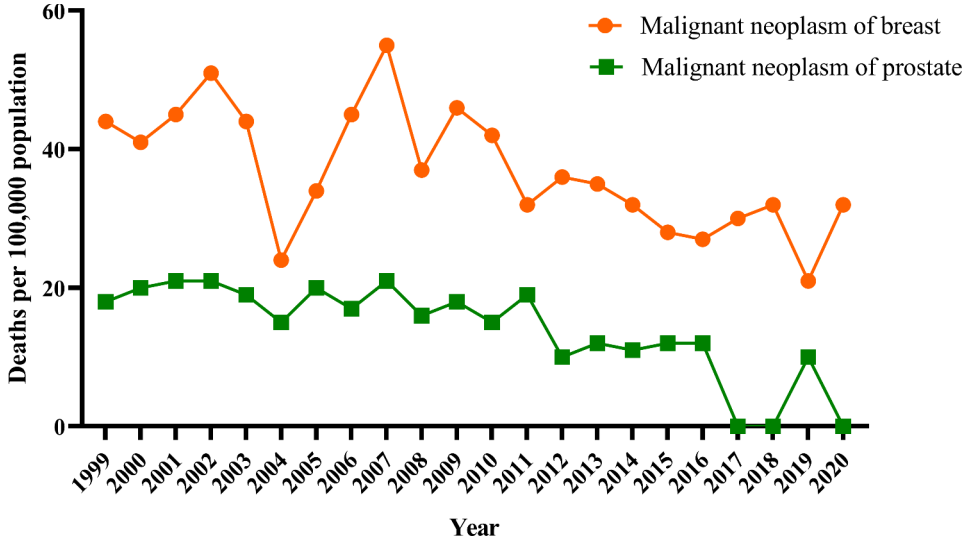

Fig. 5 The number of deaths from different comorbidities

in that respiratory diseases, neurological diseases, and tumors followed in descending order as causes of death, which contrasts with some earlier studies and suggests the need for further research to confirm these trends.

The occurrence and treatment of bone metastases in malignant tumors, particularly breast and prostate cancer, can exacerbate bone loss and increase the incidence of osteoporosis and osteoporotic fractures [35]. Osteoporosis with pathological fractures is a significant concern for survivors of breast and prostate cancer and can severely impact patient quality of life. However, the risk of low bone density varies among individuals. For instance, lumbar bone mineral density (BMD) and total hip BMD decrease by 2.76% and 4.27%, respectively, in breast cancer patients treated with tamoxifen, which is associated with an increased risk of fractures [36]. Additionally, other adjuvant treatments can raise the risk of fractures by 34% over 2.5 to 5 years [37]. Regarding prostate cancer, a cohort study of 179,744 Swedish men revealed that the use of androgen deprivation therapy was associated with a higher incidence of fractures, including hip fractures [38]. Despite the significantly increased risk of fractures and mortality in patients with breast and prostate cancer, our study found a decrease in the number of deaths over the past 22 years. This reduction may be related to the early detection of osteoporotic fractures through modern risk assessment tools, such as bone densitometry and trabecular bone score. Furthermore, early treatment interventions, including calcium and vitamin D supplementation and anti-bone resorption therapy [14], may have contributed to reducing the risk of death from osteoporosis with pathological fractures.

This study re-examined the mortality associated with osteoporosis and pathological fractures over the past 22 years. A key strength of this study is its use of MCD analysis, which allowed for the identification of the maximum possible number of deaths associated with osteoporosis and pathological fractures [39]. By categorizing these conditions as related causes of death, the analysis captured 68.3% of deaths where osteoporosis with pathological fractures was classifies as a contributing factor. The potential underestimation of rheumatic diseases in mortality statistics is attributed to complications such as infections or cardiovascular diseases, which are often identified as the underlying cause of death. This study has certain limitations. First, despite the automated processing of mortality data in the United States the task of coding causes of death is performed by trained professionals who may occasionally introduce errors or incorrect ICD-10 codes. Second, the relatively small number of deaths also precluded subgroup analyses for patients with various complications related to osteoporosis and pathological fractures. Third, relevant missing information on death certificates was not available through this system.

Conclusion

Our study indicates that older women are more frequently affected by mortality related to osteoporosis with pathological fractures compared to men. The number of deaths and mortality rates associated with these conditions has been decreasing and is anticipated to continue this trend in the coming years. Cardiovascular disease remains the primary UCD among patients with osteoporosis with pathological fractures. The observed reduction in mortality is likely attributable to advancements in diagnostic methods and the use of anti-bone resorption therapies. However, management and prevention for osteoporosis with pathological fractures remain inadequate in many countries. Therefore, it is crucial for health services to prioritize addressing mortality associated with osteoporosis and pathological fractures. Developing and implementing strategies for diagnosis and treatment can help mitigate losses and further reduce mortality among patients with these conditions.

Author contributions

RXH, CCW and YTY performed and wrote the manuscript; YY, XCH, DLM and YJH collected the references, designed the table, and drew the figures; XXH and JYL review and proofread manuscripts. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and informed consent

Not applicable.

Competing interests

The authors declare no competing interests.

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