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Research Paper

From bimodal to unimodal: The transformed incidence of osteosarcoma in the United States

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HIGHLIGHTS

- The SEER database does not demonstrate a bimodal age distribution for Primary Osteosarcoma.
- Osteosarcoma incidence peaks in 10–19 years of age.
- Primary Osteosarcoma is primarily a disease of adolescence in the Long bones. At other sites its incidence increases with age.

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ABSTRACT

Background: Osteosarcoma is the most common primary bone malignancy. It has classically been described as having a bimodal incidence by age. We sought to identify whether the bimodal incidence distribution still exists for osteosarcoma using the SEER and NIS databases.

Methods: Incidence rates of primary osteosarcoma between 2000–2021 were analyzed by age at diagnosis, year of occurrence, sex, and tumor site from the SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021). The incidence of cases in 35–64 year-olds and 65 and above was compared statistically to determine if there is an increased incidence in the later ages. Incidence of tumors of the long bones of the lower limbs from the NIS discharge database 2012–2019 was also analyzed for comparison.

Results: Overall, 5,129 cases of osteosarcoma were reported in the SEER database. Across the 22 calendar year span, a consistent first peak appeared in the second decade of life. There was no consistent second peak in the 35+ age group. There were 86,100 discharges with long bone tumors analyzed in the NIS data which exhibited nearly identical patterns.

Conclusions: Our analysis shows that the incidence of osteosarcoma is no longer bimodally distributed but rather unimodally distributed.

1. Introduction

The most common primary tumor of the bones is osteosarcoma [1]. It most commonly occurs at the long bones of the extremities and is conventionally described as having a bimodal incidence by age, with the first mode in the teenage years and the second mode after 65 years of age [2–7].

We sought to examine the more recent age distribution for the incidence of osteosarcoma. We used two large United States specific health databases: The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program which collects data on cancer incidence from various cancer registries, serving about 47.9 percent of the U.S. Population, and The National Inpatient Sample (NIS) dataset (Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality), which is the largest publicly available database of inpatient discharge data in the country [8,9].

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2. Methods

2.1. SEER

We extracted data from the SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021) [10]. SEER*Stat 8.4.3 was utilized to extract frequency and incidence rates. Data analysis and visualizations were done using Microsoft Power BI, Scipy [11] and Plotly [12]. Primary osteosarcoma cases were selected by limiting the search to patients with a) site morphology (4.1 Osteosarcoma) according to adolescents and young adults (AYA) site recode 2020 Revision and b) tumor sequence number of "one primary only" or "first of two or more". The incidence rate of primary osteosarcoma was analyzed overall, then by calendar year and finally by site.

We conducted a Fisher's exact test for each calendar year in the SEER data, assessing if there was a significant difference between the occurrence of osteosarcoma in patients *35–64 years old* versus *those 65+ years old* (the age group classically described as constituting the second peak) [3–7]. The p-values and odds ratios for the 22 calendar year period was assessed. The significance level was set at 0.05.

2.2. NIS

We also collected data from the NIS for 2012–2019 [9]. Since tumors are not classified by histological subtype within the NIS database, we used ICD-9 and ICD-10 codes which report the primary tumor location. Discharge data were extracted for *primary tumors of the long bones of the lower limbs (ICD-9: 17.07; ICD-10: C40.20, C40.21, and C40.22)* from NIS. The incidence and incidence rates of primary tumors of the long bones of the lower limbs were assessed by age for trends over 2012–2019.

3. Results

3.1. SEER

There were 5129 counts of primary osteosarcoma reported in the SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021)[10]. More cases occurred in Males (N = 2834, 55 %) than Females (N = 2295, 45 %). 40 % of all cases (N = 2049) occurred in the second decade of life with only 10 % of cases (N = 500) occurring in patients 65 and older. A histogram of Incidence Rate over the entire period reveals the first peak in the ages 10–19, with a second much smaller peak appearing at the 80–84 years group (Fig. 1). When the Age histogram for the Year 2000 is compared with that of 2021 (the most current year), a decline in incidence rate in the later years is noted (Fig. 2). These findings are confirmed in the 3D contour plot of all years (Fig. 3).

The incidence of the second peak was further investigated by performing the Fishers Exact test on the 35–64 years cohort versus the 65+ years cohort. The odds ratio of incidence showed a pattern of decline over the years from 1.6 in 2000 to 0.7 in 2021 (Table 1). Fisher's Exact Test revealed that the increased incidence in the 65+ years cohort was statistically significant (<0.05) in only 3 of the 22 years analyzed (2010, 2017, and 2019) (Table 1). Additionally, the resulting p-values tended to increase as the years, displaying a chronological trend in decreasing significance (Table 1). Review of the incidence age histogram by site (after grouping similar sites (Table 2) revealed the first peak was most prominent in long bones of the upper and lower limbs (Fig. 4). The incidence of primary osteosarcoma in other sites increased with age, however incidence at these atypical sites is too rare to form a significant second peak.

3.2. NIS

There were 86,100 discharges of tumors of the long bones of the lower limbs reported in the NIS data from 2012 to 2019 (Fig. 5), which showed close to identical trends, displaying only one peak of incidence and incidence rates in early adolescence, peaking around 10–15 years.

4. Discussion

The bimodal pattern of incidence of osteosarcoma was first proposed in a seminal single-author study published in the British Journal of Cancer in 1955. In this study, researcher C.H. Price independently analyzed 67 cases of osteogenic sarcoma, graphing their incidence [13]. Price observed two peaks in incidence, first in the 2nd decade of life and the second around the 7th and 8th decades [13]. Price followed up this work with a monograph postulating how the drastic increase in bone tumors in adolescents correlates to bone activity, since there is rapid growth and increased activity occurring at the metaphyseal plates during puberty [14]. These two studies have been pivotal in creating the current understanding of the incidence pattern of osteosarcoma.

4.1. Primary incidence peak

When assessing the overall incidence of osteosarcoma by age, we found a significant peak across all calendar years in both the SEER and NIS data sets that suggest a spike in its incidence around the onset of puberty. This is attributable to an increase in activity at the metaphyseal plates leading to the rapid increase in growth that occurs around the

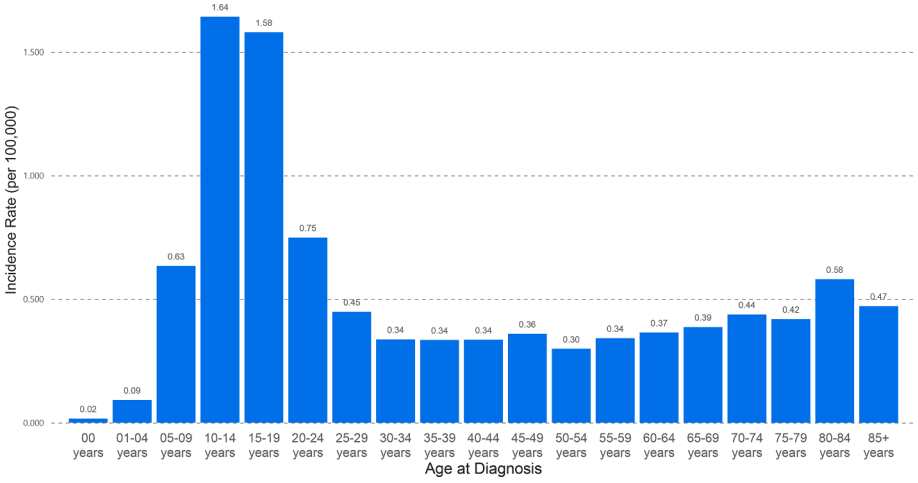

Fig. 1. Incidence Rate of Primary Osteosarcoma from SEER data over 2000–2021: Bar Diagram of the Incidence Rate of Primary Osteosarcoma based on Surveillance, Epidemiology, and End Results (SEER) SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021), by age at diagnosis.

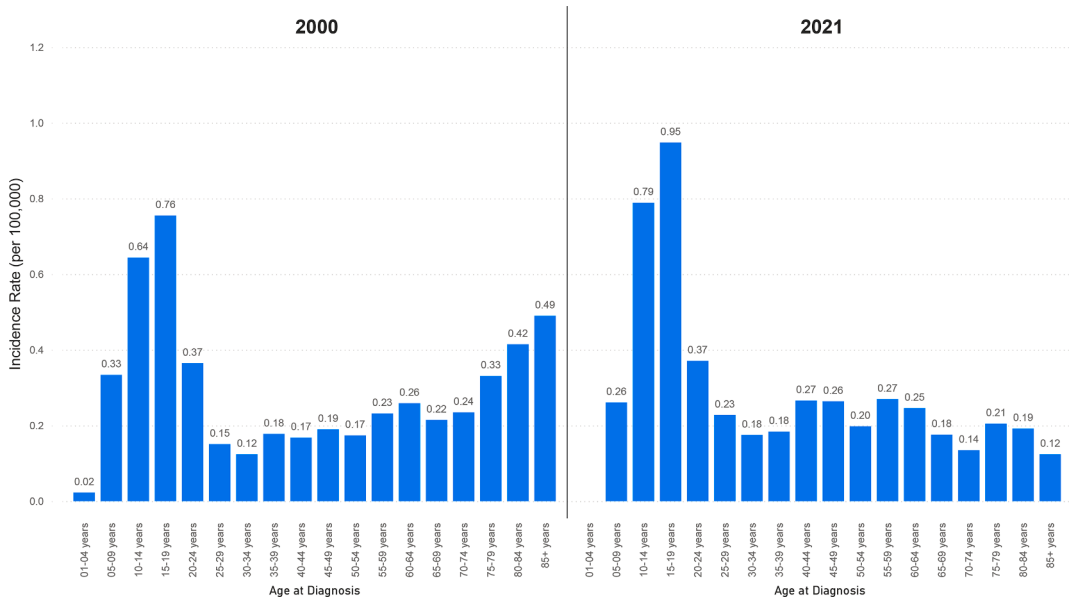

Fig. 2. Incidence Rate of Primary Osteosarcoma from SEER data in 2000 vs 2021: Bar Diagram of the Incidence Rate of Primary Osteosarcoma based on Surveillance, Epidemiology, and End Results (SEER) SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021), by age at diagnosis in 2000 (left) and 2021(right).

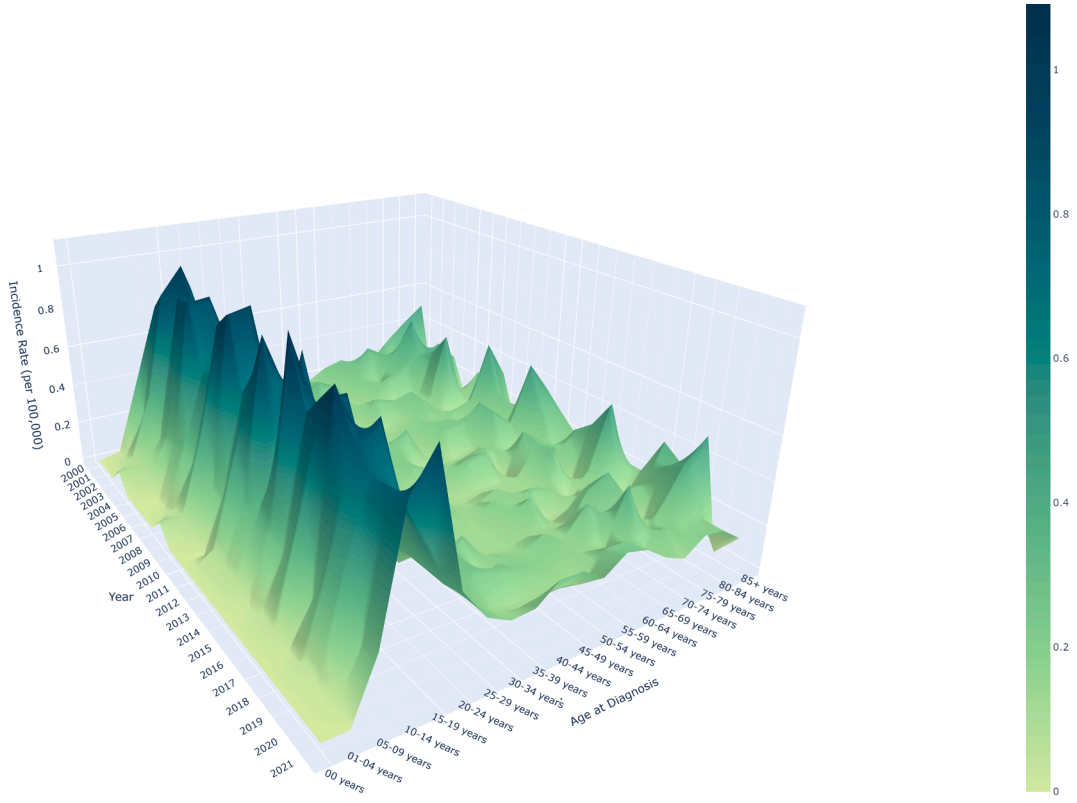

Fig. 3. 3D Graph of Incidence Rate of Primary Osteosarcoma from SEER data over 2000–2021: 3D Representation of the Incidence Rate of Primary Osteosarcoma of the long bones of the lower limbs based on Surveillance, Epidemiology, and End Results (SEER) SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021), by age at diagnosis and year of diagnosis. The darker color corresponds to an increased incidence rate of osteosarcoma reported in that age group that calendar year.

time of puberty [2,6,14]. Furthermore, the most common sites for osteosarcoma are the distal femur, proximal tibia, and proximal humerus, which are all long bones that grow significantly during puberty [4,6]. This further reinforces that osteosarcoma may be associated with increased activity at the metaphysis of bones, supporting the original theories proposed by Price [14,15].

4.2. Second incidence peak

Overall, the SEER 17 database from 2020 to 2021 lacks a second incidence peak displaying no bimodal age distribution of osteosarcoma. In contrast to the strong spike of the first peak seen in 10–19 year-olds, there is no age group in the 40+ years old sub-cohort that can consistently claim a second peak. The 3D model of the incidence rate of

Table 1
P-value Results from Fishers Test Comparing Incidence in Age Groups 35–64 years vs 65+ years in SEER data 2000–2021: P-value results from Fisher's Test for the SEER data each calendar year (2000–2021), assessing for a significance in the incidence of osteosarcoma between age groups 35–64 years and 65+ years. All significant p-values ($p < 0.05$) indicating those years where a significant difference in the incidence of osteosarcoma between the two age groups (35–64 and 65+) exists.

Year	35 to 64 Rate	65 Plus Rate	Odds ratio	p-value	
2021	0.24	0.17	0.704	0.16	
2020	0.15	0.16	1.052	0.90	
2019	0.18	0.31	1.749	0.01	*Significant
2018	0.18	0.20	1.123	0.63	
2017	0.15	0.27	1.770	0.01	*Significant
2016	0.13	0.14	1.048	0.89	
2015	0.17	0.20	1.169	0.52	
2014	0.19	0.19	0.990	1.00	
2013	0.11	0.18	1.628	0.09	
2012	0.16	0.17	1.055	0.89	
2011	0.18	0.19	1.041	0.89	
2010	0.14	0.27	1.968	0.01	*Significant
2009	0.18	0.23	1.283	0.35	
2008	0.17	0.17	1.000	1.00	
2007	0.17	0.25	1.435	0.17	
2006	0.12	0.16	1.273	0.41	
2005	0.19	0.26	1.393	0.18	
2004	0.14	0.17	1.201	0.53	
2003	0.20	0.30	1.458	0.12	
2002	0.17	0.28	1.634	0.05	
2001	0.15	0.23	1.533	0.13	
2000	0.19	0.31	1.605	0.06	

osteosarcoma (Fig. 3) represents the incidence adjusted for the population by calendar year. This model displays a strong first incidence peak consistently over all 22 calendar years, however, a consistent second peak is absent.

The declining odds ratio across the calendar years when the middle aged cohort is compared with the 65+ years cohort further confirms that the SEER osteosarcoma data is not bimodally distributed by age (Fig. 5).

4.3. Comparison to NIS data

The NIS data clearly displayed a flattening of the incidence rate in the 40+ age groups thereby reinforcing a lack of a second peak (Fig. 5). However, this only accounts for tumors of the long bone of the lower limbs which are not all osteosarcoma, though osteosarcoma overall is the most common bone tumor. For this reason, the NIS results are supportive of the SEER results but are not conclusive on their own.

4.4. Gender distribution

Our analysis using 2023 SEER 17 and NIS database revealed comparable findings with previous studies in terms of incidence rates by biological sex, though we observed an overall higher incidence of osteosarcoma in males when compared to females [7].

Historically, the occurrence of a second peak was attributed to secondary malignancy arising from pre-existing Paget's disease [2,5]. The pathogenesis of Paget's disease begins with overactive osteoclasts, promoting excessive bone resorption, and later triggering higher activity of osteoblasts, the precursor cells to osteosarcoma [16]. Today, there are highly effective pharmacotherapeutic measures for Paget's disease that specifically target reducing osteoclast function, like oral bisphosphonates and calcitonin injections, which can result in near complete control of the disease [16–18]. In particular, with the introduction of bisphosphonates around the 1970 s for the treatment of Paget's disease, there has been a noticeable decrease in the prevalence of osteosarcoma arising from this disease [17,19]. Evidence for this can be found in the Japanese population, where the development of Paget's disease is rare and a second peak has never been observed [2,20]. Thus, the change from bimodal to unimodal can be attributed to the advancements in the management of Paget's Disease in the West.

Table 2
Classification of AYA Primary Tumor Sites by Group.

Group	Sites Included	Cases Reported	Percentage
Long bones of lower limb	C40.2-Long bones of lower limb and associated joints	2986	58 %
Long bones of upper limb	C40.0-Long bones: upper limb, scapula, and associated joints	563	11 %
Bones of skull face and jaw	C41.0-Bones of skull and face and associated joints C41.1-Mandible C31.0-Maxillary sinus C05.0-Hard palate C31.1-Ethmoid sinus C31.2-Frontal sinus	448	9 %
Pelvic bones	C41.4-Pelvic bones, sacrum, Coccyx and associated joints	378	7 %
Other Bones	C41.9-Bone, NOS C40.3-Short bones of lower limb and associated joints C40.1-Short bones of upper limb and associated joints C40.9-Bone of limb, NOS C41.8-Overlap bones, joints, and art. cartilage C40.8-Overlap of bones, joints, and art. cartilage of limbs	230	4 %
Vertebrae and Ribs	C41.2-Vertebral column C41.3-Rib, sternum, Clavicle and associated joints	229	4 %
Subcutaneous Connective tissue	C49.2-Conn, subcutaneous, other soft tis: lower limb, hip C49.3-Conn, subcutaneous, other soft tis: thorax C49.1-Conn, subcutaneous, other soft tis: upr limb, shoulder C49.5-Conn, subcutaneous, other soft tis: pelvis C49.6-Conn, subcutaneous, other soft tis: trunk, NOS C49.4-Conn, subcutaneous, other soft tis: abdomen C49.0-Conn, subcutaneous, other soft tis: head, face, neck C49.9-Conn, subcutaneous and other soft tissues, NOS C49.8-Overlap conn, subcutaneous, and other soft tissues	205	4 %
Other	All Other Sites	90	2 %

Overall, these findings offer a significant shift in our understanding of the incidence of osteosarcoma with respect to age. Understanding the change in incidence might help us to better approach spreading awareness and diagnosing osteosarcoma, and likewise focus on the most affected age groups. Tracking the trends in age groups and genders affected can also help to increase our insight into potential risk factors associated with this rare neoplasm, such as environmental exposures, lifestyle measures, or other genetic associations. Developing this updated understanding of the changing age distribution for osteosarcoma occurrence can also aid in designing age-specific screening strategies and determining the limits for diagnostic tools that vary based on age and gender. While this study only investigated the occurrence of primary osteosarcoma tumors (not recurrence), there might also be a need to look at the changes in trends of recurrence of osteosarcoma as treatments have significantly changed. Prior to 1970, one of the only treatments for osteosarcoma was amputation and about 80 % of individuals died from metastases to the lungs, with a 5-year survival rate

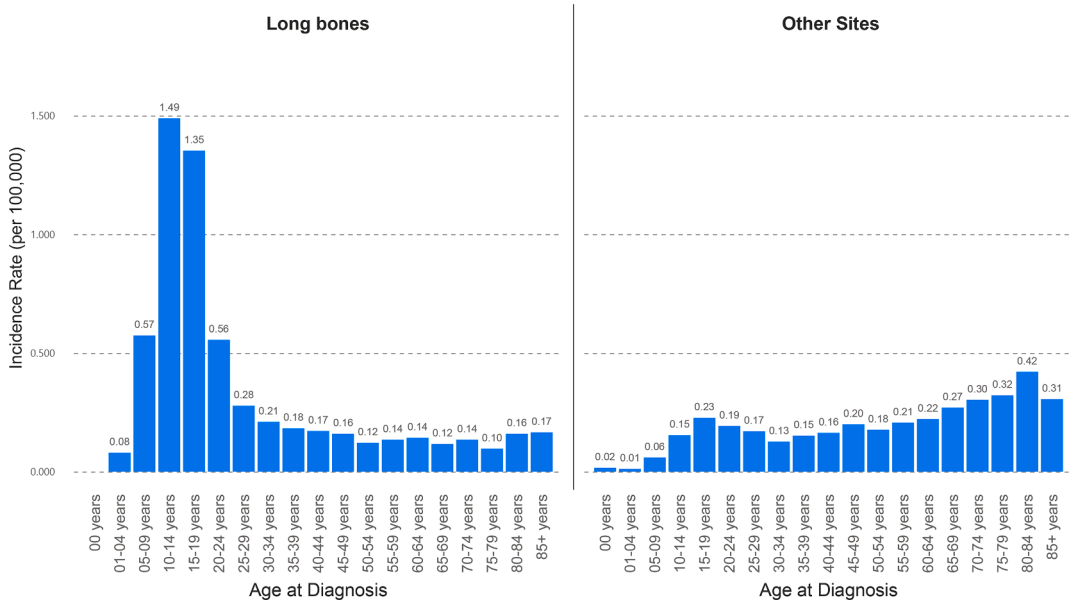

Fig. 4. Incidence Rate of Primary Osteosarcoma from SEER data in Long Bones vs Other Sites from SEER data over 2000–2021: Bar Diagram of the Incidence Rate of Primary Osteosarcoma based on Surveillance, Epidemiology, and End Results (SEER) SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021), by age at diagnosis in Long Bones (left) and Other Sites(right).

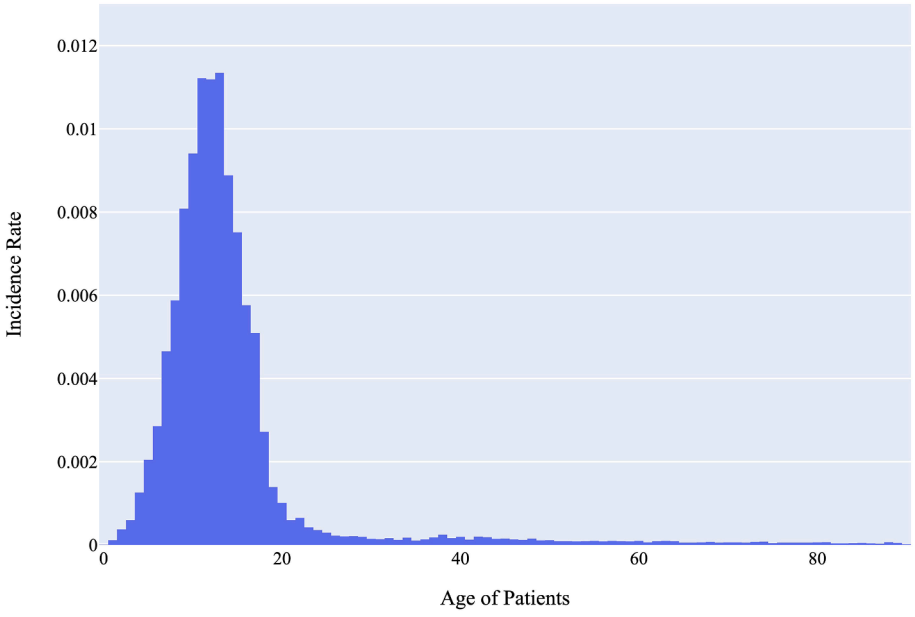

Fig. 5. Age of Patients with Tumors of Long Bone of the Lower Limbs (NIS data 2012–2019): Bar Diagram of Incidence rate of tumors of the long bones of the lower limbs based on the National Inpatient Sample (NIS) from 2012 to 2019 by age at diagnosis. The incidence rate was calculated based on the total number of tumors in each age group across the 8-year span of data.

of 20 % [4,5]. In more recent times, the treatment of choice for osteosarcoma is neoadjuvant chemotherapy, followed by limb-salvage surgery and chemotherapy [21,22]. Treatment can also include the use of newer technology like radiation [21,22]. Continuing to follow these trends in osteosarcoma will help investigate the impact of current treatment protocols and possibly offer suggestions for improvements in these therapies that might better treat the age groups affected.

5. Conclusion

Our analysis of two large US databases points toward a significant shift from the existing understanding of the bimodal incidence of osteosarcoma. Our study supports previous findings that osteosarcoma occurs more frequently in men than women. This suggests that literature must be updated to better inform healthcare providers of the true epidemiology and to focus diagnostic efforts in the teenage years while screening for osteosarcoma.

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CRediT authorship contribution statement

Emma Kar: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Amrit Ammanamanchi:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Miranda Yousif:** Writing – review & editing, Methodology, Conceptualization. **Saroja Devi Geetha:** Writing – review & editing, Methodology, Conceptualization. **Kendall Schwartz:** Writing – review & editing, Resources. **Arya Suman Mishra:** Writing – review & editing, Validation. **Jiali Ling:** Software, Formal analysis. **Kristie Nneoma Nonyelu:** Writing – review & editing. **Bijun Sai Kannadath:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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