(RESEARCH ARTICLE)

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Clinicopathological characteristics of osteosarcoma cases in a tertiary referral hospital in Indonesia: A 5-year retrospective study

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Abstract

Introduction: Osteosarcoma is the most common primary non-hematopoietic malignant bone tumor, which reportedly has a high incidence in several regions of the world including South-east Asia. However in Indonesia, the data regarding osteosarcoma trends and clinicopathological features are still lacking. Therefore, this paper aims to describe the clinicopathological features of osteosarcoma cases in a tertiary referral hospital in Indonesia.

Methods: A retrospective study of osteosarcoma cases at the Department of Anatomic Pathology of a tertiary referral hospital in East Java was conducted. Clinicopathological data regarding osteosarcoma cases diagnosed within a 5-year period (January 2018 - December 2022) were obtained. Statistical analysis were performed to the collected data.

Results: A total of 44 cases were found, with a male predominance (65.9%) and in the younger age group (11-20 years old, 36.4%). Most of osteosarcoma cases occurred in femur (50%). High grade cases predominated our cohort, with osteoblastic osteosarcoma being the most prevalent histological type (52.3%).

Conclusion: Male patients especially in younger age group predominated the cases in our center. Femur is the most common site for osteosarcoma, and most cases of osteosarcoma were of high-grade type. Osteoblastic osteosarcoma is the most common histological diagnosis in our cohort. Future larger-scale studies and nation-wide registry in order to provide better understanding and formulate the best approach for patient management are warranted.

Keywords: Osteosarcoma; Clinicopathological Features; Epidemiology; Trends; Indonesia

1. Introduction

Primary malignant bone tumors is considered a rare neoplasm, which account for <1% of cancers in adults and around 3-5% malignancies in children. The annual incidence for osteosarcoma was 3-4 patients per million population. Osteosarcoma is the most common primary non-hematopoietic malignant bone tumor (20-40% out of all bone cancers) with bimodal peaks in pediatric (2nd to 3rd decade of life) and elderly population (7th to 8th decade of life). It is defined as a high-grade intramedullary neoplasm in which the tumor cells produce and deposit osteoid matrix [1-8].

The clinical features of osteosarcoma generally consist of the appearance of a mass that enlarges quickly (within weeks to months) which often causes range of motion limitation in adjacent joints. A small number of patients (10-15%)

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present with pathological fractures. The typical radiological finding shows a permeative lytic-sclerotic lesion with bone destruction. There is non-expansive cortical destruction and periosteal reaction in the form of onion skin-like, sunburst-like, or Codman's triangle. The pathogenesis of osteosarcoma may differ depending on the histological type. In low-grade osteosarcoma and high-grade surface osteosarcoma, MDM2 and CDK4 amplification is often found. However, in conventional osteosarcoma, the pathogenesis is still unclear. There have been attempts to identify the driver gene, but this has not been determined with certainty. There is still the possibility that chromothripsis/chromoplexy is caused by an unknown trigger, which ultimately initiates chromosomal instability and tumor formation. Although the etiology is unknown, primary osteosarcoma can be associated with a number of genetic syndromes such as Li-Fraumeni and hereditary retinoblastoma. The genes that cause this syndrome are also the genes most frequently mutated in cases of sporadic osteosarcoma (TP53 in >90% of cases and RB1 in 56% of cases). Previous studies have also found that there is high immunoexpression of p53 in cases of osteosarcoma NOS [1-3]

The most common location of osteosarcoma is in long bones such as the femur, tibia and humerus, although osteosarcoma can occur in all bones. In long bones, osteosarcoma is generally found in the metaphysis (90%), and rarely in the diaphysis or epiphysis. According to the most recent World Health Organization (WHO) classification, osteosarcoma is divided into low, intermediate, and high-grade. Low-grade osteosarcomas include low-grade central osteosarcoma (LGOS) and parosteal osteosarcoma, while intermediate-grade includes periosteal osteosarcoma. Conventional osteosarcoma, telangiectatic osteosarcoma, small cell osteosarcoma, and high-grade surface osteosarcoma are included in high grade. Osteosarcoma NOS (No Other Specified) is a term that includes conventional osteosarcoma, telangiectatic osteosarcoma, and small cell osteosarcoma. Conventional osteosarcoma is further divided based on the predominant matrix into osteoblastic (76-80%), chondroblastic (10-13%), and fibroblastic (10%) types. Some uncommon pattern in conventional osteosarcoma also exist, such as the osteoblastoma-like pattern [1-3]

Across the world, the annual incidence rate varied according to age, gender, and ethnicity, with the rate being approximately 4.4 cases per 1 million people for individuals aged 0 – 24 years old, 1.7 cases per million people for those aged 25 – 59 years old, and 4.2 cases per 1 million people for those aged $\geq$ 60 years old. The highest rate for osteosarcoma cases in the first peak (people aged 10-19 years old) were observed in Northern Africa, South-eastern Asia, and South America at 9.4, 9.2, and 9.2 cases per million. Meanwhile the highest rate for osteosarcoma cases in the second peak (>60 age group) were highest in Sub-Saharan Africa with 4.9 cases per million. Males have reportedly higher incidence than females (M:F ratio 1.3 : 1). Blacks and Hispanics have higher incidence of osteosarcoma (6.8 and 6.5 cases annually per million people, respectively). Even though the incidence is relatively low compared to other cancers, osteosarcoma caused significant mortality; 5-year-survival rates for osteosarcoma is only 60-70%, and this number remains largely unchanged.[1-9]

Mortality in osteosarcoma is mainly related to metastasis. The EURAMOS-1 study showed that the 3-year and 5-year event-free survival rates for over 2000 osteosarcoma patients included in the study were 59% and 54%, respectively. Among the 621 patients which died during follow-up, 84% of deaths were attributed to osteosarcoma.[8] A study by the Cooperative Osteosarcoma Study Group (COSS) reported the that from a total of 1520 deceased patient with a history of osteosarcoma, the median time from diagnosis to death was 2.22 years, with 1286 succumbing due to osteosarcoma among which 370 patients died without complete remission and 428 patients died with more than one recurrences).[4,7]

Based on the aforementioned epidemiological data regarding osteosarcoma, it is important to establish osteosarcoma registry in order to better understand this disease and to formulate the best strategies and approach in patient management. Up until now, there has been no nationwide study depicting the epidemiology of osteosarcoma cases in Indonesia, and epidemiological studies regarding osteosarcoma in Indonesia are still scarce.[10-12] Therefore, this study aims to describe the trends of osteosarcoma cases in a tertiary referral hospital in Indonesia, as an attempt to provide insight on osteosarcoma in Indonesia.

2. Methods

A retrospective study of osteosarcoma cases at the Department of Anatomic Pathology of a tertiary referral hospital in East Java was carried out. Clinicopathological data regarding osteosarcoma cases which were definitively diagnosed using histopathology and/or immunohistochemistry examination within a 5-year period (January 2018 - December 2022) were obtained, which included age, gender, location of tumor, histological diagnosis, and tumor grade. Cases with incomplete or missing data were omitted. The data obtained were presented in tables and figures; categorical data were stated as frequencies and percentages, while continuous data were presented using mean with standard deviation (SD). This study has been approved by the Research Ethics Committee of our hospital, number 070/665/1.20/102.7/2023.

3. Results and Discussion

A total of 44 osteosarcoma cases were found. The year-wise distribution showed that there were 8 cases (18.2%) in 2018, 10 cases (22.7%) in 2019, 4 cases (9.1%) in 2020, 11 cases (25%) in 2021, and 11 cases (25%) in 2022. The frequency and percentage of osteosarcoma cases based on age, gender, and location is presented in Table 1.

Table 1 Summary of Osteosarcoma Patients' Characteristics

Characteristics	Frequency	Percentage (%)
Gender		
Male	29	65.9%
Female	15	34.1%
Age		
0-10 years old	3	6.8%
11-20 years old	16	36.4%
21-30 years old	11	25.0%
31-40 years old	4	9.1%
41-50 years old	5	11.4%
51-60 years old	4	9.1%
61-70 years old	1	2.3%
Number of cases per year		
2018	8	18.2%
2019	10	22.7%
2020	4	9.1%
2021	11	25.0%
2022	11	25.0%
Location		
Fibula	2	4.5%
Humerus	2	4.5%
Maxilla	2	4.5%
Calcaneus	1	2.3%
Tibia	12	27.3%
Femur	22	50.0%
Mandibula	2	4.5%
Iliac Wing	1	2.3%
Histological Diagnosis		
Osteoblastic Osteosarcoma	23	52.3%
Chondroblastic Osteosarcoma	5	11.4%
Teleangiectatic Osteosarcoma	1	2.3%
Small Cell Osteosarcoma	2	4.5%
Giant Cell Rich Osteosarcoma	4	9.1%
Fibroblastic Osteosarcoma	2	4.5%

Periosteal	1	2.3%
Low Grade Central Osteosarcoma	2	4.5%
Parosteal Osteosarcoma	4	9.1%

Male patients were more prevalent than female (29 vs 15 cases, respectively). Most of the patients were aged between 11 – 20 years old (16 cases, 36.4%), followed by those aged 21 – 30 years old (11 cases, 25%). The mean age was 26.73 $\pm$ 14.94, with a median of 22.5. The mean age for male patients was 24.65 $\pm$ 13.58, with a median of 21, while the mean age for female patients was 30.73 $\pm$ 17.04, with a median of 30. Age distribution of osteosarcoma cases based on gender is presented in Figure 1.
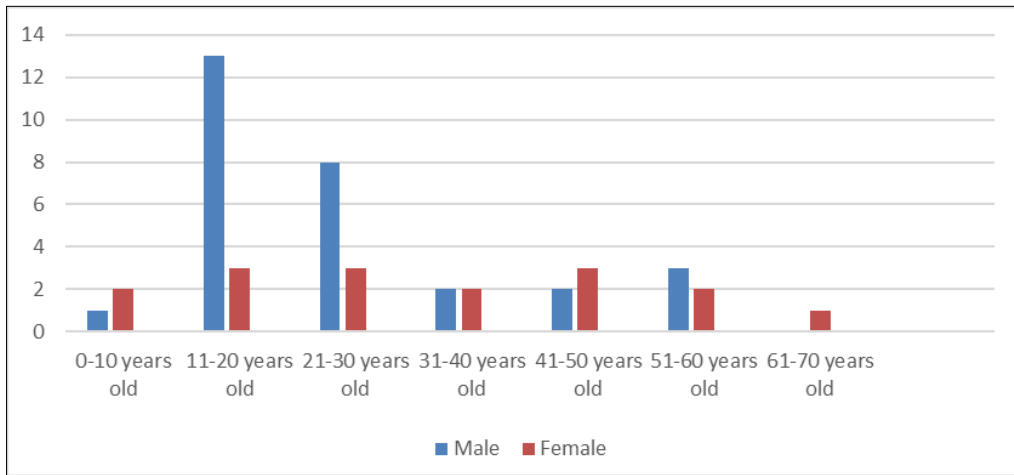

Figure 1 Age and Gender Wise Distribution of Osteosarcoma Cases

Femur was the most common for osteosarcoma in our center (22 cases, 50%), followed by tibia (12 cases, 27.3%). In our center, the most prevalent histologic type of osteosarcoma was osteoblastic osteosarcoma (23 cases, 52.3%) which also accounted for the most frequent type of high grade osteosarcoma. High grade cases were the most common, compared to intermediate and low grade cases (37 vs 1 vs 6 cases, respectively). clinicopathological characteristics of osteosarcoma in our center. Table 2 summarizes the histological type and grade of osteosarcoma cases in our center.

Table 2 Histopathological Diagnosis of Osteosarcoma Patients

Grade	Histological type	2018	2019	2020	2021	2022
High	Osteoblastic	5	7	2	3	6
	Chondroblastic	-	-	-	4	1
	Teleangiectatic	-	-	-	1	-
	Small Cell	-	1	-	1	-
	Giant Cell Rich	2	-	2	-	-
	Fibroblastic	-	-	-	1	1
Intermediate	Periosteal	-	-	-	-	1
Low Grade	LGOS*	-	1	-	1	-
	Parosteal	1	1	-	-	2
TOTAL		8	10	4	11	11
*LGOS: Low Grade Central Osteosarcoma						

Osteoblastic osteosarcoma is the most prevalent type of high-grade osteosarcoma. Table 3 describes the gender wise distribution of osteosarcoma types, while Figure 2 illustrates the age wise distribution of osteosarcoma types.
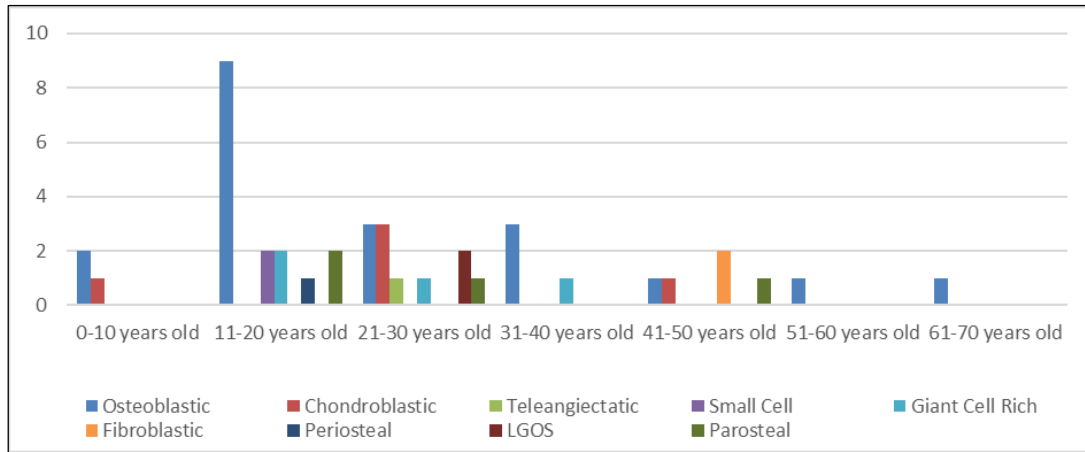
Figure 2 Age wise Distribution of Osteosarcoma Types

Table 3 Gender Wise Distribution of Osteosarcoma Types and Grades

Grade	Histological Type	Male	Female
High	Osteoblastic	15	8
	Chondroblastic	3	2
	Teleangiectatic	1	0
	Small Cell	1	1
	Giant Cell Rich	4	0
	Fibroblastic	0	2
Intermediate	Periosteal	1	0
Low Grade	LGOS*	1	1
	Parosteal	3	1
TOTAL		29	15
*LGOS: Low Grade Central Osteosarcoma			

Male predominated osteosarcoma cases in our center, and this is in accordance with the other studies which stated that osteosarcoma occur more often in males than females, particulary in puberty. In our center, the most common age group was 11 – 20 years old, which was consistent with the notion that one of the peaks for osteosarcoma is in adolescence. However, it is found that pediatric cases were more prevalent than adult or elderly cases. This is consistent with the literature which stated that juvenile osteosarcoma is more often diagnosed in South Europe, Africa, Asia, South America, and Pacific Islands. Moreover, the second peak of osteosarcoma tends to occur in elderley aged more than 60 years old, meanwhile our cohort showed that the number of elderly patients aged over 60 years old is only 1 (2.3%).[4,6]

Femur and tibia accounted for the most frequent location of osteosarcoma cases in our center, and this is in accordance with other literatures which stated that the most common site of origin for osteosarcoma is femur, tibia, and humerus. Unusual or less common sites for osteosarcoma such as jaw, iliac wing, and calcaneus were also mentioned in the literature, and were also present in our center in few cases. Figure 3 presents the age and location wise distribution of osteosarcoma, while Table 4 describes the location wise distribution of osteosarcoma types. Tumors of the jaw typically presents in 3rd to 4th decade of life; patients with maxillar and mandibular osteosarcoma in our center were also in the 3rd to 5th decade of life. Osteoblastic osteosarcoma is the most common histological type in our cohort, in concordance with other literature in Indonesia and other countries which reported that conventional osteosarcoma, especially the osteoblastic type, is the most common type of osteosarcoma to exist. A study regarding chondroblastic osteosarcoma revealed that it has a male predominance, and a mean age of 20 years old. The patients in our center revealed a slight male predominance, with 3 cases occuring in male versus 2 cases occuring in females. Chondroblastic osteosarcoma of

our cohort occurred in a wide age range, from the 1st to 5th decade of life. In our cohort, teleangiectatic osteosarcoma was found in a male patient, in his 3rd decade of life; literature stated that teleangiectatic osteosarcoma is usually found in the 2nd decade of life with a male predominance. Small cell osteosarcoma were found in a female and a male patient, both in their 2nd decade of life, while in the literature it is stated that small cell osteosarcoma may occur in a wide age range (5-83 years old), but has a preponderance in pubertal period with a slight female predominance. Other study also mentioned that more than half of small cell osteosarcoma cases occur in the long bone, which is in agreement with our cohort of small cell osteosarcoma cases in tibia. Giant cell rich osteosarcoma is a rare variant of osteosarcoma which has been reported to be found mostly in the young adults with a mean age of 26 year old, and located in the long bones and craniofacial bones. In our center, giant cell rich osteosarcoma were found in 4 male patients in their 2nd-4th decade of life.[1-3,13-20].
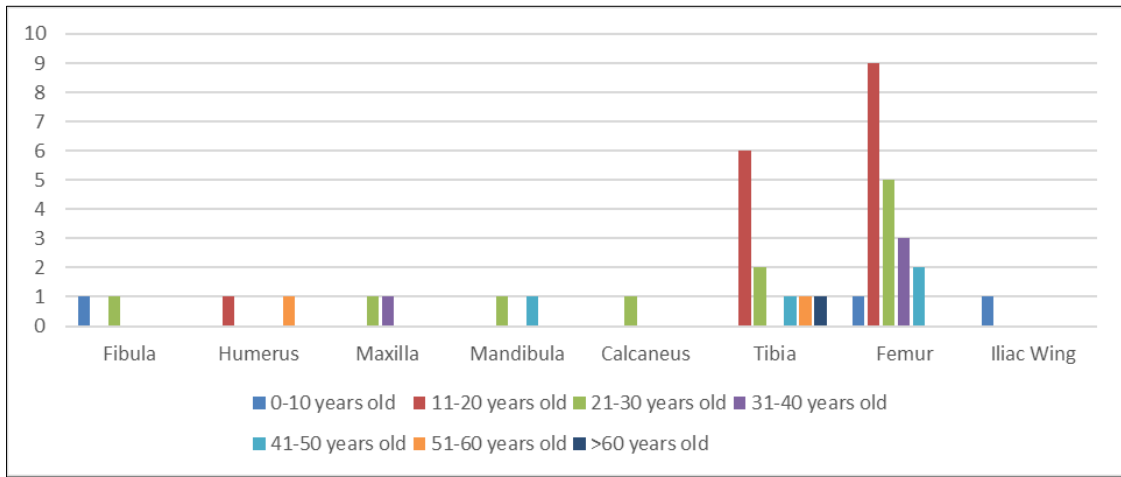

Figure 3 Age and Location Wise Distribution of Osteosarcoma

Table 4 Location Wise Distribution of Osteosarcoma Types and Grades

Grade	Type	Fibula	Humerus	Maxilla	Calcaneus	Tibia	Femur	Mandibula	Iliac Wing
High	Osteoblastic	1	2	-	1	6	13	-	-
	Chondroblastic	-	-	-	-	-	2	2	1
	Teleangiectatic	-	-	-	-	-	1	-	-
	Small Cell	-	-	-	-	2	-	-	-
	Giant Cell Rich	1	-	1	-	1	1	-	-
	Fibroblastic	-	-	-	-	1	1	-	-
Intermediate	Periosteal	-	-	-	-	1	-	-	-
Low Grade	LGOS*	-	-	1	-	1	-	-	-
	Parosteal	-	-	-	-	-	4	-	-
TOTAL		2	2	2	1	12	22	2	1
*LGOS: Low Grade Central Osteosarcoma									

Periosteal osteosarcoma is an intermediate-grade osteosarcoma which account for <2% of all osteosarcoma cases with a peak incidence in the 2nd decade of life and balanced male to female ratio. In our study, there was only 1 case of periosteal osteosarcoma (2.3%) in a male patient on his 2nd decade of life. There are two types of low-grade osteosarcoma, namely parosteal osteosarcoma and LGOS. Parosteal osteosarcoma accounts for 4% of all osteosarcoma cases, while LGOS accounts for 1-2% of cases. Both of these entities usually occur in young adults on their 3rd decade of life, with a slight female predominance. In our cohort, parosteal osteosarcoma occurred in 4 patients: 3 males and 1 female, among which 2 were in the 2nd decade of life, 1 was in the 3rd decade of life, and the other one was in the 5th

decade of life. Meanwhile, LGOS cases in our center were found in 2 patients, 1 male and 1 female, both in their 3rd decade of life.[1-3]

The limitations of this study are the small number of cases, as this is a single-center study. Therefore, it may not fully reflect the epidemiology of osteosarcoma cases in Indonesia and difficult to draw definitive conclusion from this study. Nevertheless, this study may paint a picture in the osteosarcoma trends of our region and hopefully may encourage the establishment of osteosarcoma registry in Indonesia. Up until now, there has been no nationwide study depicting the epidemiology of osteosarcoma cases in Indonesia, and internationally-publicized literature regarding osteosarcoma in Indonesia are still scarce. Larger scale and nationwide studies are warranted.

4. Conclusion

This study showed that osteosarcoma cases in our center is predominated by male patients and younger age group. Femur is the most common site for osteosarcoma, and most cases of osteosarcoma were of high-grade type. Osteoblastic osteosarcoma is the most common histological diagnosis in our cohort. Future larger-scale studies and nation-wide registry in order to provide beter understanding and formulate the best approach for patient management are warranted.

Compliance with ethical standards

Acknowledgement

Disclosure of Conflict of Interest

The authors declare no conflict of interest.

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