International Journal of Health Science and Technology e-ISSN 2685-8673
Vol. 5, No. 2 (2023), pp. (174-182)
10.31101/ijhst.v5i2.3259

Original Research

Analysis of the effect of age and residence on the incidence of Giant Cell Tumors

Yuni Prastyo Kurniati[1*], Ikhya' Izatus Zahro[2], Yusuf Alam Romadhon[3]
[1] Department of Anatomical Pathology, Faculty of Medicine, Jl. A. Yani, Pabelan, Kartasura, Sukoharjo, Jawa Tengah 57169 Universitas Muhammadiyah Surakarta, Indonesia
[2] Faculty of Medicine, Universitas Muhammadiyah Surakarta, Jl. A. Yani, Pabelan, Kartasura, Sukoharjo, Jawa Tengah 57169, Indonesia
[3] Department of Public Health, Faculty of Medicine, Universitas Muhammadiyah Surakarta, Jl. A. Yani, Pabelan, Kartasura, Sukoharjo, Jawa Tengah 57169, Indonesia
ypk134@ums.ac.id

Submitted: September 3, 2023 Revised: October 27, 2023 Accepted: November 29. 2023

Abstract
Giant cell tumors are benign neoplasms that damage bone and often recur and have aggressive lesions. Benign tumors that can transform into malignant, aggressive, and able to metastasize to other organs.These tumors range from 3-8% of primary bone tumors in Western populations and as many as 20% in Asian countries. Risk factors for this disease are more common in women and at the age of the second to fourth decade. However, there are differences about the distribution of rural and urban areas between countries, as well as the age distribution of patients with these tumors in some countries. The purpose of this study was to analyze the effect of age and residence on the occurrence of Giant Cell Tumor. This study used a cross-sectional research design. The study sample was a histopathology preparation taken from 107 patient medical record data according to inclusion criteria using purposive sampling techniques. The results of the study found subjects with the most GCT were found in the high-risk age group (age range 20 to 50 years) of 67.3% and most of them lived in urban areas as much as 81.3%. Fisher's test showed an influence of age on the incidence of giant cell tumors ($p = 0.007$) and no influence between residence and the incidence of giant cell tumors ($p = 0.262$). The conclusion of this study is that age has a significant effect on the occurrence of Giant cell tumors. Meanwhile, residence does not affect the occurrence of Giant cell tumors.

Keywords: age; bone; giant cell tumor; residence

1. Introduction

Giant cell tumor (GCT) is a type of benign neoplasm that destroys bone, characterized by multinucleated osteoclast-like giant cells with osteolytic properties scattered among neoplastic stromal cells (di Carlo et al., 2020; Raharjo & Setiawati, 2022). This tumor belongs to the group of generalized neoplasms that account for 4-5% of all primary bone tumors (Herdini et al., 2022) . Giant Cell Tumor is a benign tumor that can transform into malignant, aggressive, and able to metastasize to other organs (Maulida et al., 2023). Malignant GCT occurs in about 2-9%. Previous studies have reported that local recurrences and metastases to distant organs are common. This makes the prognosis worse (Zhu et al., 2021) . GCT is a rare tumor, but its occurrence is not known with certainty (Verschoor et al., 2018). In western countries, these lesions account for 3-8% of all primary bone tumors, but in Asia they are more common with an incidence of 20% (Futriani et al., 2022; Lin et al., 2016) . The incidence of GCT varies by region. These tumors range from 3-8% of primary bone tumors in Western populations and 20% in Asian countries. The incidence rate of giant cell tumor of bone in the Netherlands is 1.7 per million population per year (Verschoor et al., 2018). While in China the incidence rate is 1.47 per

million population per year, higher than in the United States (1.38 per one million population per year) and Japan (1.25 per one million population per year). The figures show 2094 new cases in China, 160 in Japan, and 447 in the United States in 2017. Giant cell tumors of bone can affect all races, but a higher prevalence of 20-30% is found in populations in China and India (Maulida et al., 2023). Data from Riskesdas in 2018 shows the prevalence of cancer incidence in Indonesia is 1.49% (Ministry of Health of the Republic of Indonesia, 2019). Research conducted at Sanglah Hospital Denpasar in 2013-2015 showed the prevalence of this case amounted to 53.3% of all benign bone tumor cases (Desrianta & Wiratnaya, 2020). These lesions are more common in men with a ratio of 1.12:1, and most patients are aged 20 to 40 years (Pradana & Edward, 2021; Zhang et al., 2021) . The prevalence of giant cell tumors peaks in the third decade, with about 80% of cases occurring between the ages of 20 and 50. These tumors often occur in the second to fourth decades with the highest peak of cases in the fourth decade as much as 31.1% (Putra et al., 2021). However, there were also reports of 10 cases of patients with giant cell bone tumors aged more than 55 years (Broehm et al., 2018; Orosz &; Athanasou, 2017; Pujani et al., 2015). As many as 3% of cases occur at the age of less than 14 years, and only 13% occur in patients over 50 years old (Chakarun et al., 2013). Different things are found in GCT sufferers in China. A systematic review showed findings that the average age of diagnosis of GCT was 35.7 years in the population in China (Liede et al., 2018). A study conducted at Hasan Sadikin Hospital Bandung found data that GCT bone tumors were most commonly found in women aged 20 to 29 years and around 32 years in men (Gunasegaran et al., 2016) . A systematic review, which found that the incidence in China is more than four times that in Japan and the United States, suggests diagnostic errors, differences in rural and urban distribution between countries, and a younger age distribution may be contributing factors to GCT more often affecting young individuals (20-40 years) (Liede et al., 2018).

The most frequent locations of these tumors are around the knee region, distal femur, proximal tibia, distal radius, and sacrum (Hu et al., 2016; Sobti et al., 2016). The problem of evaluating risk factors for giant cell tumors in bone is associated with the very rare incidence of these tumors. In an epidemiological study in Sweden based on medical records in the period 1983 – 2011 found the incidence of this tumor was 1.3 cases per one million population per year, while the highest incidence in the age range of 20 – 39 years was 2.1 cases per one million population per year (Amelio et al., 2016). The literature review study used data from 4 large studies, all of which reported case series to collect 2135 patients (Palmerini et al., 2019). A simple bibliometric analysis conducted by the authors, using a scopus data base with the keywords "giant cell tumor of bone" AND "risk factors analysis" with limitations on "human", "medicine", "multidisciplinary", "risk factors", "epidemiology", research on giant cell tumor of bone, began in the data base in 1990. The number of studies from 1990 – 2024 is only 111 documents, with the 5 largest countries having the number of research in the field: China 33 documents, America 19 documents, Italy 13 documents, Japan 13 documents, and the Netherlands 9 documents. From this description, analysis of age and environmental risk factors for the incidence of giant cell tumor of bone in Indonesia is still very limited. Thus, the purpose of the study set is to analyze age and environmental factors in this case rural and urban residences on the proportion of the incidence of Giant cell tumor of bone with comparison of Benign abnormalities of non-giant cell tumor bone.

2. Research Methods

This study is an analytical observational study with a cross-sectional approach. The research sample used histopathological preparations sent to the Anatomical Pathology laboratory of Medical Faculty UMS, equipped with medical record data from Dr. Soeharso Surakarta Hospital throughout 2019-2020 which met the inclusion inclusion criteria using the purposive sampling principle. The preparation used is a sample with a diagnosis of Anatomical Pathology of benign bone tumors in accordance with the WHO classification and the origin of the residence of special patients in the Java Island region. This

study obtained a total of 107 preparations, consisting of 47 samples with giant cell tumors and 60 others with non-GCT diagnoses. The non-GCT group consists of a mixture of diagnoses of chronic inflammation of Granulomatous et causa Tuberculosis, and benign bone tumors other than GCT, e.g. Osteochondroma and Aneursymal Bone Cyst. The variable data of age and residence used is in accordance with the date of birth and address listed in the medical record. The high-risk age category is the age range of 20 to 50 years. While the low-risk age is the age range of less than 20 years and or more than 50 years. The criteria for housing that include Urban are high-density population concentration areas and modern facilities and most of the population works outside agriculture. Conversely, those who fall into the category of rural areas are those where most of the population works on agricultural / agrarian land. These criteria are adjusted to the information in the Central Bureau of Statistics. Furthermore, the data was processed using the SPSS program to determine the normality of data distribution, as well as univariate and bivariate analysis using Fisher's test.This research has received approval by the Health Research Ethics Commission (KEPK) FK UMS with No. 3841/B.1/KEPK-FKUMS/IX/2021.

3. Results and Discussion

A total of 107 patients met the inclusion criteria in the study. A total of 43.1% (47 patients) were diagnosed with GCT with the highest percentage of cases in the age group of 20-50 years, namely 67.3% (72 patients). Based on residence, most patients live in urban areas as much as 81.3% (87 patients).

Table 1. Univariate characteristics of research samples

Sample Characteristics	n	%
Diagnosis Group		
GCT	47	43,9
Non-GCT	60	56,1
Age		
Low risk (<20 years and > 50 years)	35	32,7
High risk (20 years to 50 years)	72	67,3
Residence		
Rural (rural)	20	18,7
Urban	87	81,3
Gender		
Man	49	45,8
Woman	87	54,2

Source: Secondary data, 2022

Based on the table above, samples that had a GCT diagnosis were 43.1% (47 patients). Based on age, the highest frequency of bone tumors was in high-risk groups with an age range of 20 to 50 years as much as 67.3% (72 patients). Meanwhile, based on residence, most bone tumor patients are in urban areas, which is 81.3% (87 patients). While sex characteristics are more commonly found in women, which is 54.2%. These results are in accordance with those mentioned by WHO. Some literature mentions that this tumor is often found in the age group of young adults between the ages of 20 and 40 years. A study on the GCT population in the Netherlands also states that the average age of these tumors appears between 20 and 40 years (Verschoor et al., 2018). WHO said the peak of the incidence of these tumors was in the age category of 20 years to 45 years, only about 10% of which were found in the second decade of age. Some references say that this disease is more common in women than men (Kurniati, 2021; World Health Organization, 2018). A systematic review found that in Sweden's cancer

registry data, GCT has a higher incidence prevalence in people living in urban areas at 73%, compared to rural areas at 23% (Amanatullah et al., 2014) .

Table 2. The effect of Age on the incidence of Giant cell tumors

Age	GCT		Non-GCT		OR	p
	N	%	n	%		
Low risk (<20 and >50 years)	9	25.7	26	74.3	3.229	0.007
High risk (20-50 years)	38	52.3	34	47.2		

Source: Secondary Data, 2022

The proportion of the age group 20 – 50 years who suffer from GCT is greater than the age group <20 years and > 50 years, with a value of OR = 3,229. The results of the Fisher test for the analysis of the effect of age on the incidence of GCT showed a p-value of 0.007. This shows that there is a significant influence between age and the incidence of GCT.

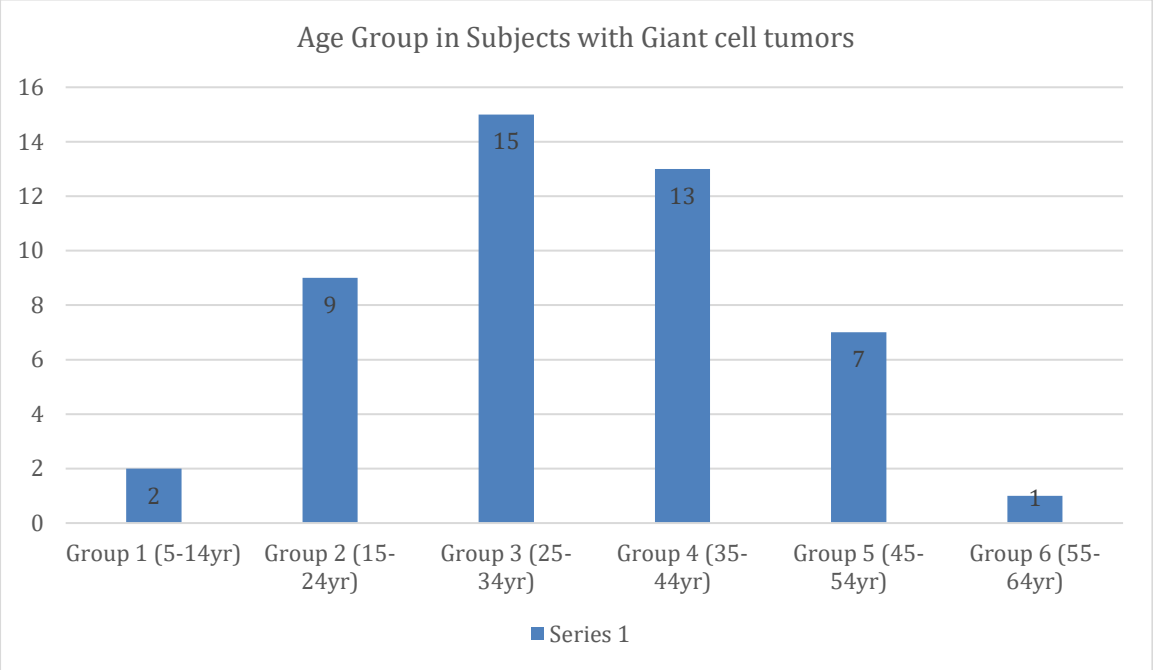

Figure 1. Age Group in subjects with Giant cell tumors

Source: Secondary data, 2022

The findings of this study as seen in figure 1 showed the highest frequency in 15 patients at the age of the third decade, followed by the age of the fourth decade which amounted to 13 subjects. This means that a total of 28 out of 47 GCT bone tumor patients were found by the age of the third and fourth decades. These results are almost similar to those found in China. The average incidence of GCT occurs at the age of 35 years with the highest number of cases at the age of 20 to 39 years in the country (Hu et al., 2016). A systematic review said the average age of GCT diagnosis in the Chinese population was 35.7 years (Liede et al., 2018). A study on GCT at Hasan Sadikin Hospital Bandung mentioned almost similar results. The tumor is found most at the age of over 19 years with the highest incidence at the age of the third decade. Bone GCT is most commonly found in women aged 20 to 29 years and around age 32 years in men (Gunasegaran et al., 2016). Research in Bali found similar findings that lesions are more common in the second to fourth decades (Putra et al., 2021). According to WHO, the peak incidence occurs at the age of 20 to 45 years and about 10% of cases occur in the second decade of life (World Health Organization, 2018) . Some literature explains that this is because GCT occurs in skeletal mature bone (Gunasegaran et al., 2016; Liede et al., 2018). These tumors rarely appear in

immature bones (immature skeleton) (World Health Organization, 2018). These lesions are generally more common in young adult individuals who are skeletally mature (Kim et al., 2021; Liede et al., 2018) .

Slightly different results were obtained in the age distribution of patients in the population in the Netherlands. The age distribution of people with these tumors appears to be bimodal with peak incidences between 20 and 39 years and between 50 and 59 years (Zhu et al., 2021). The results of the study review in three countries Sweden, Australia and Japan GCT incidence 1.03 – 1.33 cases per million population per year, with an age range of 20 – 40 years (Liede et al., 2014) . Another review of studies in Sweden found a GCT incidence of 1.3 cases per million inhabitants per year, with a median age of 34 years (range 10 – 88 years) (Amelio et al., 2016) . The Dutch study using the national pathology registry found an incidence of GCT of 1.66 per million inhabitants per year, with a median age of 35 years (range 9 – 77 years) (Verschoor et al., 2018) .

The next result was a residential analysis with the incidence of Giant Cell Tumor. The division of residence classification is based on population density per km2, percentage of farming families, and presence or access to urban facilities, owned by a village or kelurahan to determine its status (Central Bureau of Statistics, 2020). Table 3 below shows how residence affects the incidence of giant cell tumors.

Table 3. The Effect of Residence on the Incidence of Giant Cell Tumors

Residence	GCT		Non-GCT		OR	p
	N	%	N	%		
Rural	7	35.0	13	65,0	1.581	0.262
Urban	40	46.0	47	54.0		

Source: Secondary data, 2022

There is no difference in the proportion of GCT sufferers between rural and urban. The results of the Fisher test for the analysis of the effect of residence and GCT showed a p-value of 0.262.

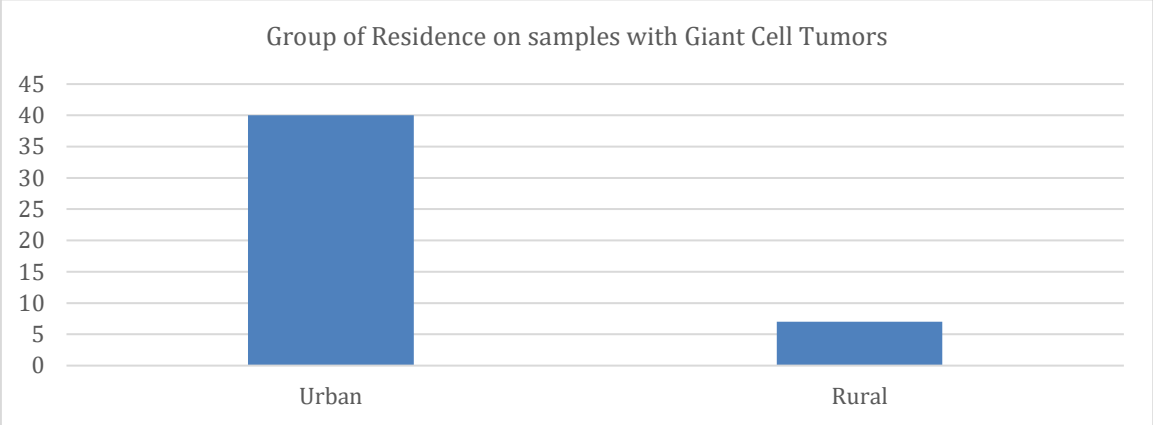

Figure 2. Group of Residence on samples with Giant Cell Tumors

Source: Secondary data, 2022

The results of subsequent studies showed that residence with urban and rural area classifications did not have a significant relationship with the occurrence of these lesions (p = 0.262). In this study, the most distribution of GCT patients was in the cities of Pati, Semarang, Cilacap, Sukoharjo, Brebes, and Purbalingga. The area is a mainstay area in the industrial sector (Pujiati, 2009). The findings in this study showed that as many as 40 subjects from 47 respondents with GCT lived in urban areas (urban). This is similar to that found by a Swedish study of the 1958-1968 pathology registry which found the prevalence of GCT in urban areas at 73%, compared to rural areas with a percentage of 23%

(Amanatullah et al., 2014; Larsson et al., 1975) . This is possible in relation to the negative impact of industrial activities, namely the increased concentration of pollutants coming from factory chimneys (Turyanti et al., 2016). A review of studies that evaluated such large differences in GCT incidence between China, Japan and the United States at 2,094, 160 and 447 respectively in 2017, found that one of these differences was related to urban and rural demographic variations (Liede et al., 2018) .

Giant cell tumor of Bone is a bone tumor that usually occurs in long bones in young adults. More than 95% of mutations occur in the H3F3A gene that codes for histone H3.3 (Isidor et al., 2015). Benign tumors that can turn out to be malignant, aggressive, and capable of metastasis to other organs. A distinctive feature of GCT is monomonoplastic mononuclear monoplastic stroma mixed with macrophages and osteoclast-like giant cells. Overactivity of nucleated giant cells results from overactivity of nuclear factor-kappa β ligand receptor activators (RANKL), which are expressed in stromal cells (Maulida et al., 2023; Shibuya et al., 2020) . Here is a picture of lesions in this type of tumor.

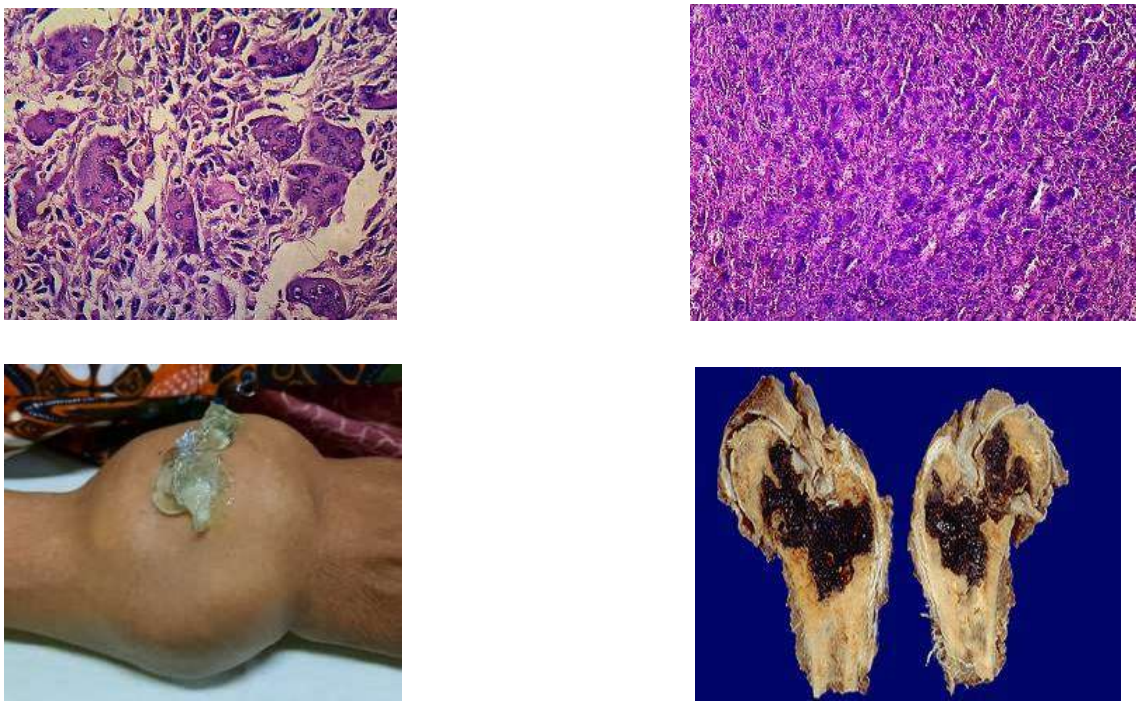

Figure 3. Microscopic (top) and macroscopic (bottom) images of giant cell tumors. Microscopic many found multinucleated giant cells, with osteoclast type

Source: Personal documentation, 2019

The RANK pathway is often reported to be involved in the pathogenesis of GCT. This pathway is an important signaling pathway in bone remodeling that plays an important role in the differentiation of precursors into multinucleated osteoclasts and the activation of osteoclasts leading to bone resorption (López-Pousa et al., 2015). The kappa B [NF-kB] nuclear factor ligand receptor activator (RANKL) is important for GCT pathogenesis. Under normal physiological circumstances, osteoclast formation requires interaction with cells of osteoblastic derivatives, which may depend on contact of cells, and interaction of RANKL with its receptor RANK. These receptors are highly expressed on monocytes, whereas RANKL is expressed by various types of cells, including stromal cells and lymphocytes (Chenliang et al., 2020). Various co-regulatory molecules also take part in the formation of osteoclasts, including monocyte colony-stimulating factor, vitamin D, parathyroid hormone and proteins related to parathyroid hormone, and prostaglandins. Some studies identify RANKL as highly expressed by stromal cells in GCT. Stromal cells also secrete factors that can regulate or prevent osteoclastogenesis,

including osteoprotegerin, which blocks osteoclast/osteoblast interactions and serves as a natural negative regulator of RANKL (Avnet et al., 2013). RANKL expression by osteoblast-like mononuclear stromal cells stimulates osteoclastic cell recruitment from normal monocytic pre-osteoclast cells. The osteoclastic giant cells then actively absorb the host bone through cathepsin K-mediated processes and matrix metalloproteinase 13, which would explain the osteolysis associated with these tumors (Maulida et al., 2023).

Another risk factor of this tumor is the presence of genetic mutations. The transformation process in this lesion is an H3F3A (H3.3) mutation involving glycine 54 which codes for Gly34Trp and 1 which codes for changes in Gly34Leu. Histone H3.3 mutations are found in stromal cell populations, and not in osteoclasts or their precursors (Skubitz, 2014). In addition, this disease is found to be more common in women than men (Kurniati, 2021; World Health Organization, 2018). While in this study the sex characteristics were almost the same between men (45.8%) and women (54.2%).

4. Conclusion

The conclusion of this study is that the age factor has a significant effect on the incidence of Giant cell tumors with a value of p = 0.007. Meanwhile, residence does not have a significant effect on the incidence of Giant cell tumors with a value of p = 0.262. The most subjects were in the at-risk group with an age range of 20 to 50 years as much as 67.3% and more lived in urban areas as much as 81.3%. Research on tumor history in kinship and family as well as environmental socio-demographic factors in subjects with GCT tumors still needs to be explored in depth as a follow-up research.

Acknowledgments

The researcher expressed his gratitude to SMF Orthopedic Oncology and the Anatomical Pathology Laboratory of Dr. Soeharso Surakarta Orthopaedic Hospital, as a national referral hospital for Bone and Musculoskeletal cases, for providing support and assistance. Acknowledgments were also conveyed to the support staff at the Anatomical Pathology Laboratory, Faculty of Medicine, University of Muhammadiyah Surakarta.

References

Amanatullah, D. F., Clark, T. R., Lopez, M. J., Borys, D., & Tamurian, R. M. (2014). Giant cell tumor of bone. *Orthopedics*, *37*(2), 112–120. https://doi.org/10.3928/01477447-20140124-08

Amelio, J. M., Rockberg, J., Hernandez, R. K., Sobocki, P., Stryker, S., Bach, B. A., Engellau, J., & Liede, A. (2016). Population-based study of giant cell tumor of bone in Sweden (1983-2011). *Cancer Epidemiology*, *42*, 82–89. https://doi.org/10.1016/j.canep.2016.03.014

Avnet, S., Salerno, M., Zini, N., Alberghini, M., Gibellini, D., & Baldini, N. (2013). Sustained autocrine induction and impaired negative feedback of osteoclastogenesis in $CD14^+$ cells of giant cell tumor of bone. *American Journal of Pathology*, *182*(4), 1357–1366. https://doi.org/10.1016/j.ajpath.2012.12.021

Badan Pusat Statistik. (2020). *Peraturan Kepala BPS No 120 Tahun 20220 Tentang Klasifikasi Desa, Perkotaan, dan Perdesaan di Indonesia 20201, Buku 2, Jawa*.

Broehm, C. J., Inwards, C. Y., Al-Ibraheemi, A., Wenger, D. E., Jenkins, S. M., Jin, L., Oliveira, A. M., Zreik, R. T., Carter, J. M., Boland, J. M., Boland, J. M., & Fritchie, K. J. (2018). Giant Cell Tumor of Bone in Patients 55 Years and Older. *American Journal of Clinical Pathology*, *149*(3), 222–233. https://doi.org/10.1093/ajcp/aqx155

Chakarun, C. J., Forrester, D. M., Gottsegen, C. J., Patel, D. B., White, E. A., & Matcuk Jr, G. R. (2013). Giant cell tumor of bone: review, mimics, and new developments in treatment. *Radiographics*, *33*(1), 197–211.

Chenliang, L., Zhenqun, Z., & Wanlin, L. (2020). The role of OPG/RANKL/RANK signaling pathway in the pathogenesis of giant-cell tumor of bone. *Chinese Journal of Tissue Engineering Research*, *24*(23), 3723–3729. https://doi.org/10.3969/j.issn.2095-4344.2694

Desrianta, I. G. N., & Wiratnaya, I. G. E. (2020). Prevalensi Tumor Tulang Jinak Di Rumah Sakit Umum Pusat Sanglah Denpasar Tahun 2013-2015. *Medika Udayana*, *9*(11), 110–114.

di Carlo, F. S., Whyte, M. P., & Gianfrancesco, F. (2020). The two faces of giant cell tumor of bone. *Cancer Letters*, *489*, 1–8.

Futriani, Muhammad P. Johan, Ni Ketut Sungowati, Andi A. Zainuddin, Djumadi Achmad, & Upik A. Miskad. (2022). Clinical Characteristics of Giant Cell Tumour of Bone in Makassar, Indonesia. *International Journal of Sciences: Basic and Applied Research (IJSBAR)*, *62*(2), 177–181. https://www.gssrr.org/index.php/JournalOfBasicAndApplied/article/view/14103

Gunasegaran, K., Irawan, M. N. S. B., & Yantisetiasti, A. (2016). Epidemiology of Giant Cell Tumor in Dr. Hasan Sadikin General Hospital Bandung from 2010-2013. *Althea Medical Journal*, *3*(2), 244–247.

Herdini, C., Yudistira, D., & Indrasari, S. R. (2022). Maxillary Giant Cell Tumor in Jogjakarta, Indonesia: A Case Report. *2nd Global Health and Innovation in Conjunction with 6th ORL Head and Neck Oncology Conference (ORLHN 2021)*, 59–61.

Hu, P., Zhao, L., Zhang, H., Yu, X., Wang, Z., Ye, Z., Wu, S., Guo, S., Zhang, G., & Wang, J. (2016). Recurrence rates and risk factors for primary giant cell tumors around the knee: a multicentre retrospective study in China. *Scientific Reports*, *6*(1), 36332.

Isidor, B., Odri, G., Gouin, F., & Heymann, M.-F. (2015). Genetics of giant cell tumors of bone. In *Bone Cancer: Primary Bone Cancers and Bone Metastases: Second Edition*. https://doi.org/10.1016/B978-0-12-416721-6.00029-7

Kementerian Kesehatan Republik Indonesia. (2019). *Laporan Nasional Riset Kesehatan Dasar 2018*.

Kim, W.-J., Kim, S., Choi, D.-W., Lim, G.-H., & Jung, S.-T. (2021). Characteristics of giant cell tumor of the bone in pediatric patients: Our 18-year, single-center experience. *Children*, *8*(12). https://doi.org/10.3390/children8121157

Kurniati, Y. P. (2021). Giant Cell Tumor Of Small Bone: Kasus Tumor Tangan yang langka. *Prosiding University Research Colloquium*, 958–965.

Larsson, S. E., Lorentzon, R., & Boquist, L. (1975). Giant-cell tumor of bone. A demographic, clinical, and histopathological study of all cases recorded in the Swedish Cancer Registry for the years 1958 through 1968. *JBJS*, *57*(2). https://journals.lww.com/jbjsjournal/fulltext/1975/57020/giant_cell_tumor_of_bone__a_demographic,_clinical,.7.aspx

Liede, A., Bach, B. A., Stryker, S., Hernandez, R. K., Sobocki, P., Bennett, B., & Wong, S. S. (2014). Regional Variation and Challenges in Estimating the Incidence of Giant Cell Tumor of Bone. *JBJS*, *96*(23). https://journals.lww.com/jbjsjournal/fulltext/2014/12030/regional_variation_and_challenges_in_estimating.9.aspx

Liede, A., Hernandez, R. K., Tang, E. T., Li, C., Bennett, B., Wong, S. S., & Jandial, D. (2018). Epidemiology of benign giant cell tumor of bone in the Chinese population. *Journal of Bone Oncology*, *12*(July), 96–100. https://doi.org/10.1016/j.jbo.2018.07.003

Lin, F., Hu, Y., Zhao, L., Zhang, H., Yu, X., Wang, Z., Ye, Z., Wu, S., Guo, S., & Zhang, G. (2016). The epidemiological and clinical features of primary giant cell tumor around the knee: A report from the multicenter retrospective study in china. *Journal of Bone Oncology*, *5*(1), 38–42.

López-Pousa, A., Broto, J. M., Garrido, T., & Vázquez, J. (2015). Giant cell tumour of bone: new treatments in development. *Clinical and Translational Oncology*, *17*(6), 419–430. https://doi.org/10.1007/s12094-014-1268-5

Maulida, A. I., Ramzi, A., Kayla, B. G., Nadila, C., Salsabila, D., Anggy, F., Fesmia, H. L., Rahma, J. A., Putri, T. A. K., & Fakar, W. A. (2023). Giant Cell Tumor: Pathogenesis and Clinical Manifestation. *Jurnal Biologi Tropis*, *23*(4b), 193–199.

Noh, B.-J., & Park, Y.-K. (2018). Giant cell tumor of bone: updated molecular pathogenesis and tumor biology. *Human Pathology*, *81*, 1–8. https://doi.org/10.1016/j.humpath.2018.06.017

Orosz, Z., & Athanasou, N. A. (2017). Giant Cell–Containing Tumors of Bone. *Surgical Pathology Clinics*, *10*(3), 553–573. https://doi.org/10.1016/j.path.2017.04.004

Palmerini, E., Picci, P., Reichardt, P., & Downey, G. (2019). Malignancy in Giant Cell Tumor of Bone: A Review of the Literature. *Technology in Cancer Research & Treatment*, *18*, 1533033819840000. https://doi.org/10.1177/1533033819840000

Pradana, I. P. G. P., & Edward, M. (2021). Giant cell tumor of the ribs: a case report. *Journal Orthopaedi and Traumatology Surabaya*, *10*(1), 32–38. 10.20473/joints.v10i1.2021.32-38

Pujani, M., Bahadur, S., Jairajpuri, Z. S., Jetley, S., & Jameel, J. (2015). Giant Cell Tumor Bone in an Elderly Male- an Unusual Case Misdiagnosed on MRI as a Malignant Sarcoma. *Indian Journal of Surgical Oncology*, *6*(3), 285–287. https://doi.org/10.1007/s13193-015-0408-x

Pujiati, A. (2009). Analisis Kawasan Andalan in Central Java. *Analisis Kawasan Andalan Di Jawa Tengah Analisis Kawasan Andalan in Central Java AMIN*, *11*(2), 117–128.

Putra, I. K. B. A., Sumadi, I. W. J., Sriwidyani, N. P., & Ekawati, N. P. (2021). Karakteristik Klinikopatologi Giant Cell Tumor Tulang di RSUP Sanglah Denpasar Bali tahun 2008 - 2018. *Jurnal Medika Udayana*, 24–27.

Raharjo, P., & Setiawati, R. (2022). Diagnosis of bone giant cell tumor in elderly patient: A case report of an unusual case. *Annals of Medicine and Surgery*, *79*, 104111.

Shibuya, I., Takami, M., Kawamoto, M., Karakawa, A., Nakamura, S., & Kamijo, R. (2020). Immunohistochemical analysis of the distribution of rankl-expressing cells and the expression of osteoclast-related markers in giant cell tumor of bone. *Journal of Hard Tissue Biology*, *29*(3), 137–146. https://doi.org/10.2485/jhtb.29.137

Sobti, A., Agrawal, P., Agarwala, S., & Agarwal, M. (2016). Giant cell tumor of bone-an overview. *Archives of Bone and Joint Surgery*, *4*(1), 2.

Turyanti, A., Tania, J., Edvin, A., & Erliza, N. (2016). Analisis Pola Dispersi Partikulat Dan Sulfurdioksida Menggunakan Model Wrfchem Di Sekitar Wilayah Industri Tangerang Dan Jakarta. *Jurnal Manusia Dan Lingkungan*, *23*(2), 169–178.

Verschoor, A. J., M G Bovée, J. V, L Mastboom, M. J., Sander DIJKSTRA, P. D., J Van De Sande, M. A., & Gelderblom, H. (2018). Incidence and demographics of giant cell tumor of bone in The Netherlands: First nationwide Pathology Registry Study. *Acta Orthopaedica*, *89*(5), 570–574. https://doi.org/10.1080/17453674.2018.1490987

World Health Organization. (2018). *WHO Classification of Tumors*.

Zhang, X.-P., Lu, X.-C., Wang, L.-L., Wei, J.-Q., Yan, J., Shao, X.-N., Che, Y.-Y., & Cheng, J.-L. (2021). Giant Cell Tumors of Bone in Patients Aged 18 Years Old or Younger: Imaging Features and Tumor Characteristics. *International Journal of General Medicine*, 8389–8397.

Zhu, X., Huang, R., Hu, P., Yan, P. D., Zhai, S. A., Zhang, J. F., Zhuang, J. E., Yin, H. A., Meng, T. F., Yang, D. A., & Huang, Z. (2021). *Prognostic Factors for Survival in Patients with Malignant Giant Cell Tumor of Bone: A Risk Nomogram Analysis Based on the Population*. https://doi.org/10.12659/MSM.929154