ORIGINAL ARTICLE

Evaluating the REST Scoring Method (Radiological Evaluation Score for Bone Tumors) as a Novel Radiological Tool in Distinguishing Benign and Malignant Bone Tumors: Accuracy Study at a Tertiary Referral Hospital

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ABSTRACT

Introduction: The misdiagnosis due to high mimicking of bone tumor malignancy and uneven access to advanced examinations in rural areas are yet several problems in bone tumor examinations. Not to mention, the high morbidity and mortality rates indicate obstacles to these cases. This study analyses the accuracy of X-rays processed using a new modality, Radiological Evaluation Score for Bone Tumors (REST) in primary bone tumor patients at Dr. Soetomo Regional Hospital Surabaya. **Methods**: This study was an analytical observational study that analyzed the correlation between each scoring criterion and its total score with histopathology (biopsy) results, calculated the cut-off value for benign and malignant type scoring, and diagnosis accuracy. The sample totaled 142 samples by a total sampling technique. Analysis calculation and variables were explained in the chapter. **Discussion**: Based upon the obtained p values, it showed that 1) there was no correlation between age, cortical erosion, and pathological fractures with histopathological results ($p \geq 0.05$); 2) there were correlation between gender, characteristic, tumor content, lesion boundaries, transition zone, periosteal reaction, connective tissue mass, and the total scoring with histopathological results ($p < 0.05$); 3) the cut-off value was 3.5; 4) the diagnostic accuracy was 85.3%. The kappa value for interobserver reliability was 0.764. **Conclusion**: The correlation of REST scoring with the histopathology results has shown dominantly significant with considered good diagnostic accuracy. These results have demonstrated a promising future development for the utilization of X-ray as bone tumour diagnosis modality.
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INTRODUCTION

While primary bone tumors are relatively uncommon afflictions, they nonetheless present a considerable burden in terms of morbidity and mortality rates since the 1970 (1,2). 70% of individuals afflicted with bone cancer manage to survive beyond five years and this drastically decreases to a mere 20–30% for patients with metastasis or poor responders to therapies3. Moreover, 30% to 40% of them experience a recurrence within two to three years post-treatment significantly diminishes the 5-year survival rate to 20% (3). As a result, these phenomena have caused bone tumor cases to stagnate in survival rates over the past four decades, despite advancements in treatments. Several studies also showed the hindrance on health experts in treating bone tumors in the field and therefore paramount to achieve effectiveness and efficiency of diagnosis and management of bone tumors (1,4,5).

Although examination for the diagnosis of bone tumors is carried out using the histopathological evaluation as the gold standard, biopsy carries several risks of infection, impaired wound healing, until economic and social factors (6,7). Furthermore, in a 2022 study in the

United States, it was found that only 38.84% of rural areas had access to point-of-care ultrasound compared to 88.56% of metropolitan areas and 74.19% of all areas (5). This reveals the lack of access to advanced radiology examinations in rural areas. On top of that, there is a high number of misdiagnoses due to the mimicking of non-tumorous (inflammation, osteomyelitis, etc.), benign, and malignant bone tumor lesions (8,9). Mimicking phenomenon of bone malignancies even shown in advance imaging, such as conventional MRI in differentiating osteosarcoma and osteomyelitis (17). Misdiagnosis, especially of malignant bone tumors, can lead to a higher risk of metastasis, more severe complications, and risks in the surgical process (10). In conclusion, the utilization of radiographic examination, such as X-ray imaging, may need to be implemented as an efficacious diagnostic modality, capable of excluding numerous differential diagnoses, evaluating, and managing bone tumor patients.

Looking from a journal created in 2022 by Salunke, et al., the journal researched and composed a REST scoring system consisting of 8 criteria, namely characteristics, content, cortical breach, distinctiveness, distribution (zone of transition), periosteal reaction, soft tissue mass, and fracture of the bone. Remarkably, the diagnostic precision studied in the first cohort of 100 samples was proved to be exceptionally high, boasting in 99% accuracy rate. Radiological scoring system has been evolving and benefit clinicians, another study by Setiawati Rosy, et al., proving an X-ray scoring system help determine disease progression especially in areas with shortages of facilities and specialists (16). This study aimed to study and measure the accuracy of the REST scoring system to differentiate benign and malignant bone tumors in Dr. Soetomo Regional Hospital that has never been carried out before to ascertain the efficacy of this scoring system function.

Subjects and Methods

Radiological Evaluation Score for Bone Tumors (REST)

The REST scoring system assigns a score to a given set of radiographs based on eight radiological factors into a single score. Each radiological factor within this scoring system is assigned a value of 0 or 1, contingent upon the radiological findings (10). For each patient, a clear X-ray photograph and the final histopathology report of their lesion were documented. The diagnosis of each sample follows the standardized terminology and diagnostic framework provided by the World Health Organization (WHO) which is the gold standard for the classification of bone and soft tissue tumors, as referred to WHO Classification of Tumours of Soft Tissue and Bone or WHO Blue Book (18).

Study Population and Inclusion Criteria

This was an observational analytic study and was conducted at the Diagnostic Center Building of Regional Hospital Dr. Soetomo, Surabaya, Indonesia after approval by the institutional ethical committee. Samples were retrospectively identified from the period between January 2020 and June 2023. The sample selection process encompassed all clinical patients presenting with suspected bone tumors who underwent radiographic examination of the extremities and/or pelvis in anteroposterior and/or lateral projections, in conjunction with histopathological results. This cohort was confined to those receiving treatment during the same period. REST scoring system process were selected from a final cohort of 142 patients (Figure 1) and underwent a blinded scoring process twice, each by two experienced radiologists.

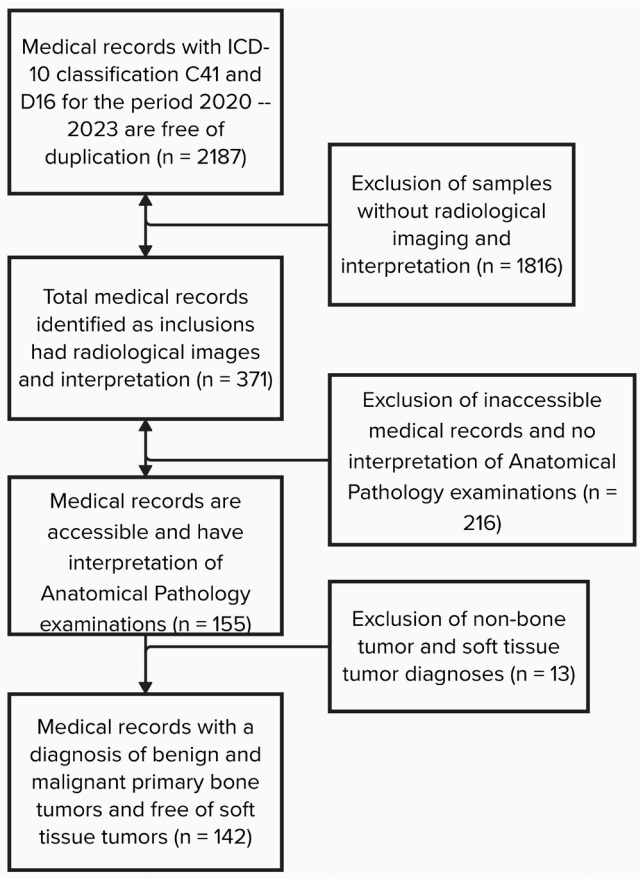

Figure 1: Flowchart of the study profile showing inclusion and exclusion criteria to identify final cohort sample.

Statistical Methods

Statistical analyses were performed using the SPSS statistical package version 21.0 and Microsoft Excel. Bivariate analysis by the Chi-square test and Independent T-test was used to establish correlations between sample demographics, between variables, as well as between the scores and the gold standards outcome (benign or malignant). A p value of less than 0.05 was considered statistically significant. Score results from the final cohort (n=142) were measured by intraclass correlation coefficient (ICC) with 95% confidence interval and Cohen's Kappa to identify the quality of interobserver agreements. The statistical validity of the

scoring system and other factors underwent assessment utilizing sensitivity and specificity. The sensitivity and specificity outcomes were subsequently compared employing a receiver operator characteristic (ROC) curve. Additionally, cross-tabulation and histogram of scores and outcomes were constructed to forecast both modalities. Cut off value of the scoring system between benign and malignant was determined by the ROC curve and Youden Index method. Finally, diagnostic accuracy were calculated using the 2x2 table method.

Results

Radiological Evaluation Score for Bone Tumors (REST)
General characteristics assessed from the study sample shown in Table 1. The research sample was mostly aged 20-29 years with a total sample of 44 (30.1%) and an average age of 26.96 ± 14.48 years. Of the total sample of 142 samples, 41.5% (59 people) of the samples had benign bone tumour histopathology results and 58.5% (83 people) were benign. The most common bone tumor histopathology type distribution was GCT and osteosarcoma. Tumor types classified as benign and tumor types classified as malignant. Based on the demographics, bone tumor was most likely occur at age 20 - 29 years as shown in Figure 2. Benign bone tumor was found to be most common in the age group of 20 - 29 years, while malignant type was most common at age 10 - 19 years (Figure 2). In males, the most common diagnosis in bone tumor patients was osteosarcoma (25.6%), while in females was giant cell tumour (26.67%).

Table I: Characteristics of Research Sample

No	Variable	Sample (n=142)
1	Age	
	0—9 years old	7 (4,93%)
	10—19 years old	43 (30,3%)
	20—29 years old	**44 (30,1%)**
	30—39 years old	23 (16,2%)
	40—49 years old	6 (4,2%)
	50—59 years old	16 (11,3%)
	60—69 years old	2 (1,4%)
	>70 tahun	1 (0,7%)
	P value (Chi-Square Test)	0.0045 (<0.01)
2	Gender	
	Male	60 (42,3%)
	Female	82 (57,8%)
	P value (Chi-Square Test)	0.017 (<0.05)
3	Tumor location	
	Antebrachii	1 (0,6%)
	Calcaneus	3 (1,9%)
	Cruris	3 (1,9%)
	Femur	**46 (28,4%)**
	Fibula	4 (2,5%)
	Humerus	24 (14,8%)
	Metacarpal	4 (2,5%)
	Olecranon	3 (1,9%)
	Pelvis	3 (1,9%)
	Phalang	6 (3,7%)
	Radius	10 (6,2%)
	Ileum	1 (0,6%)
	Pubis	6 (3,7%)
	Sacrogluteal	1 (0,6%)
	Scapula	4 (2,5%)
	Tibia	37 (22,8%)

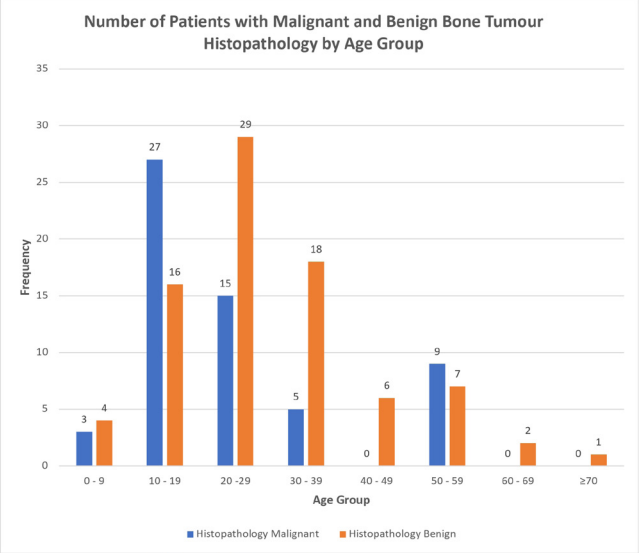

Figure 2: Cross-Tabulation between Patient Age Group and Bone Tumor Histopathology.

Inter-observer Reliability

All 142 sample assessments made by the observers were analyzed with intraclass correlation coefficient statistics to compare scoring as well as Cohen's kappa to compare prediction of benign or malignant diagnosis. we found the ICC value was 0.985 (95% CI 0.979-0.989, p-value <0.001), so the result was that there was significant inter-observer agreement beyond chance between the scores and predictions of the assessors. For the comparison of histopathology prediction of benign and malignant bone tumours among observers, we found a Cohen's kappa value of 0.764 (95% CI 0.69-0.84) with a p value of <0.001 indicating strong agreement which is unlikely to be due to chance as a factor. From the Cohen's Kappa and ICC values, the study can be continued.

Overview of the Eight REST Scoring Criteria and Other Variables in the Research Sample

The following is the correlation between the study variables consisting of age, gender, and 8 (eight) scoring criteria as radiological parameters with the histopathological results of samples classified into benign bone tumours and malignant bone tumours. The REST scoring assessment was conducted on a sample of 142 and obtained a distribution of scoring values with an average score of 3.68 ± 2.071 (mean ± standard deviation). As for the histopathology-confirmed benign bone tumour group, the mean score was 2.45 ± 1.042 (mean ± standard deviation) with a range of 0-6, SD 1.042, 95% CI 2.21-2.68, while in the histopathology-confirmed malignant bone tumour group, the mean score was 5.42 ± 1.886 (mean ± standard deviation) with a range of 1-8, SD 1.886, 95% CI 4.93-5.92 (Figure 3).

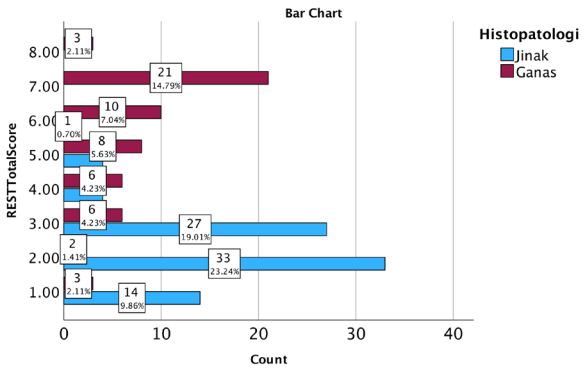

Figure 3: Histogram between REST Total Score and Bone Tumor Histopathology.

Cut Off Scoring Determination

The ROC curve is a statistical element that can compare the accuracy of the scoring system against each variable (eight criteria listed in REST Scoring). The area under the curve was 0.89 (95% CI 0.827 - 0.953) indicating good discrimination of the two groups of scores or good tests. The cut-off value of the results of the REST scoring study using the ROC curve and Youden Index method is intended to obtain a score distinguishing radiograph images with malignant results and benign results. With the ROC curve for REST scoring, the furthest point of the curve was found to be sensitivity = 0.814 and 1 - specificity = 0.108 which matches the cut-off score of 3.5. The researchers also performed an optimal cut-off value selection technique with Youden Index, the highest was at a cut-off value of 3.5000, so the REST Scoring matched a cut-off score of 3.5.

Analysis of Each Criteria in the REST Scoring System

The researchers correlated the accuracy of each criterion using ROC curves for each radiological criterion, namely characteristics (AUC 0.72; 95% CI 0.63 - 0.8), tumour content (AUC 0.7; 95% CI 0.6 - 0.78), cortical erosion (AUC 0.52; 95% CI 0.42 - 0. 61), lesion boundary (AUC 0.87; 95% CI 0.8 - 0.93), transition zone, (AUC 0.86; 95% CI 0.79 - 0.93) periosteal reaction (AUC 0.687; 95% CI 0.6 - 0.78), connective tissue mass (AUC 0.63; 95% CI 0.54 - 0.72), and pathological fracture (AUC 0.52 95% CI 0.43 - 0.62). It was found that lesion boundary, transition zone, characteristics, and tumour content criteria had higher accuracy (area under ROC curve 0.7 - 0.8) than periosteal reaction, connective tissue mass, fracture, and cortical erosion criteria (area under ROC curve 0.5 - 0.6).

Diagnostic Accuracy of REST Scoring System in Tertiary Hospital

By using cross-tabulation, we can display the sensitivity (true positive), false positive, false negative, and specificity (true negative) of REST scoring correlated with histopathology results as the gold standard of bone tumor diagnosis as described below: 1) Sensitivity/ True Positive = 81.4%; 2) False Positive = 10.8%; 3) False Negative = 18.6%; 4) Specificity/True Negative = 89.2%. A positive predictive value of 84.2% and a negative predictive value of 87.1% were also obtained. This indicates a high true positive value among all positive values and a high true negative value among all negative values. The diagnosis accuracy of the REST scoring was 85.3%.

Scoring Model

A model was created for applying the REST scoring system to two sample X-ray images that provided the Radiological Evaluation Score for Bone Tumors (REST) values. We pick one representative imaging of osteolytic character with cortical destruction (geographic destruction type 1B) at epi-meta-diaphysis of upper third of left tibia, showing multiple lytic lesions, with no periosteal reaction, no calcified matrix, and narrow transition zone. This sample was given diagnosis based on histopathological results of giant cell tumour at upper left cruris (Figure 5; Table 2)

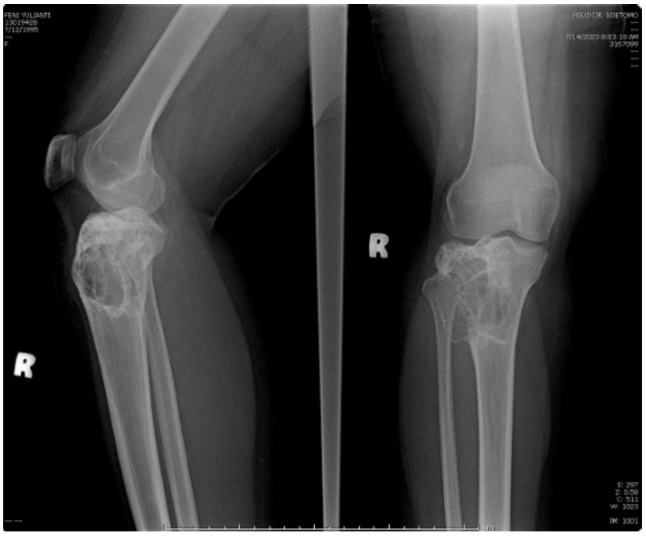

Figure 5: Sample with histopathological diagnosis of Giant Cell Tumour at Upper Left Cruris

Table II: REST scoring model for figure below with cortical destruction characteristics (geographic destruction type 1B) at epimetadiaphysis of upper 1/3 of left tibia, multiple lytic lesions, no periosteal reaction, no calcified matrix, and narrow transition zone

Radiological **E**valuation **S**core for Bone **T**umors **(REST)**				
Radiological Criteria	Interpretation	Score (0)	Interpretation	Score (1)
Characteristics of tumor	Osteolytic	0	Osteoblastic/ Mixed	-
Content of tumor	Mineralization/ Calcification present	0	Not present	-
Cortical erosion	Absent	-	Present	1
Distinctiveness	Well defined	0	Ill defined	-
Distribution (zone of transition)	Narrow zone of transition	0	Wide zone of transition	-
Periosteal reaction	Absent or benign-type periosteal reaction	0	Present	-
Soft Tissue Mass	Absent	0	Present	-
Pathological fracture	Absent	0	Present	-
Total Score (Minimum = 0; Maximum REST : 1 by 8 (1/8) = 8)				
Score interpretation *Score < 3 = suggestively benign bone tumor* (True = *bold format*) *Score 3 = suggestively malignant bone tumor*				

*Radiograph imaging regarding the REST Score Table is in Figure 5

Discussion

In this study, researchers analyzed the correlation of the scoring system and other variables with histopathological outcomes, assessed cut-off scores, and determined the diagnostic accuracy of a scoring system for assessing radiographs from patients with suspected bone tumors, namely REST or an acronym for Radiological Evaluation Score for Bone Tumors. This scoring system is a proposed test from a research study in Italy, in 2022 (Salunke et al., 2022) that claims to be a new approach to differentiating bone tumor lesions into benign and malignant tumors. In the current score, we have included the same eight radiological parameters as the criterias and validated it on 142 patients with primary bone tumors, a higher number from previous first study of the REST scoring system. The REST score differ significantly between the two groups based on total score ROC curve and cut-off value determining method by the Youden Index. With a REST of > 3 strongly predictive of a malignant bone lesion and a score of < = 3 suggesting a benign tumor, the current investigation helped identify individuals with a malignant bone lesion. A higher REST indicated a greater likelihood of a malignant bone tumor.

Criteria Breakdown

The tumor's characteristics (osteolytic, osteoblastic, or mixed) and content (absence of mineralization or presence of osteoid/chondroid) act as indicators of its origin or constituent of the tumor. While so, the characteristic and content tumor criteria in the current study were significantly different between benign and malignant groups (both p-values <0.001). Extensive cortical breakthrough was said to be suggested as malignancy. Cortical expansion is otherwise most commonly seen in benign bone tumors with slow enough growth to allow the cortex to be totally or partially intact (11). Malignancies (for the most part) are more likely to progress rapidly and destroy rather than expand the cortex. We observed that cortical erosion was found in 88% of benign lesions and 92% of malignant lesions.

The transition zone's width and border definition classify lesions as slow-growing and benign (narrow, well-defined) or rapid-growing and potentially malignant (wide, less defined). Three main types of radiographic margins have been described by Lodwick classification, where type 1A describes benign lesions or tumors; type 1B which are intermediate, benign, or malignant, aneurysmal bone cysts, and low-grade malignant tumors; type 1C predominantly malignant tumors; types II and III are non-geographic and consist of ill-defined areas of bone destruction (11). In the current study, the wide zone of transition and ill-defined lesions were highly associated with the malignant bone lesions.

Based on a study by Osborne the benign features are lesions with clear borders, sclerotic rim, and thick unilamellar periosteal reaction, whereas periosteal reaction with permeated and spiculated pattern is aggressive. In the current study, periosteal reactions are present in 54% of malignant cases and absent in 83% of benign cases, whereas soft tissue masses are present in 80% of malignant cases and 54% of benign cases (15).

Inter-observer Reliability

In the current study, we had two observers who underwent blinded scoring of REST to total samples. We performed Cohen's Kappa and intraclass correlation coefficient to measure scoring reliability on continuous variables and consisted of two observers. The ICC value was 0.985 (95% CI 0.979-0.989, p-value <0.001), so the result is that there is significant inter-observer agreement beyond chance between the scores and predictions of the observers. In addition, Cohen's kappa value was 0.764 (95% CI 0.69-0.84) with a p-value of <0.001 indicating strong agreement which is unlikely to be due to chance.

REST Scoring Cut-Off and ROC Curve

The REST scoring assessment was conducted on a sample of 142 and obtained a distribution of scoring values with a mean score of 3.68 ± 2.071 (mean ± standard deviation). In the histopathology-confirmed benign bone tumor group, the mean score was 2.45 ± 1.042 (mean ± standard deviation) with a range of 0 - 6, SD 1.042, 95% CI 2.21-2.68, while in the histopathology-confirmed malignant bone tumor group, the mean score was 5.42 ± 1.886 (mean ± standard deviation) with a range of 1 - 8, SD 1.886, 95% CI 4.93-5.92. Based on the study conducted by Salunke et al. (2022), shows that the scoring results of samples with bone tumors at Dr. Soetomo Regional Hospital have a higher average score

of benign tumors and a lower average score of malignant tumors so that the distance between the average values of the two groups is shorter. The range of the two groups of tumors from REST scoring performed on patients at RSUD Dr. Soetomo Surabaya overlaps at a value of 1 - 6, while in the study conducted by Salunke et al. (2022), the range of the two tumor groups overlapped at a value of 2 - 3. This affects the diagnostic accuracy of the scoring system.

If the confidence interval results are relatively narrow (0.7 - 0.8), the mean standard deviation of the sample is likely to match the population12. In this study, the CI of the benign bone tumor group scoring had an interval (2.68 - 2.21) of 0.47, showing relatively narrow interval values, so the average scoring data of both bone tumor groups are relevant in practice or have clinical significance. It was also found that the CI of the malignant bone tumor group scoring had an interval (5.92 - 4.93) of 0.99, indicating that there is still sufficient probability despite the greater uncertainty, i.e. the probability of a different mean when taking other samples in the population.

The AUC (area under curve) was 0.89 (95% CI 0.827 - 0.953) indicating good discrimination of both groups of scores or a good test (Figure 4). The AUC or area under the ROC curve illustrates the REST scoring to distinguish scoring subjects who have malignant or benign bone tumors. In addition to interpreting the AUC value, researchers also evaluate the 95% confidence interval which reflects the uncertainty surrounding the AUC value. A narrow confidence interval (CI) (interval 0.7 - 0.9) indicates that the AUC value is most likely accurate, while a wide CI indicates that the AUC value is less reliable (12).

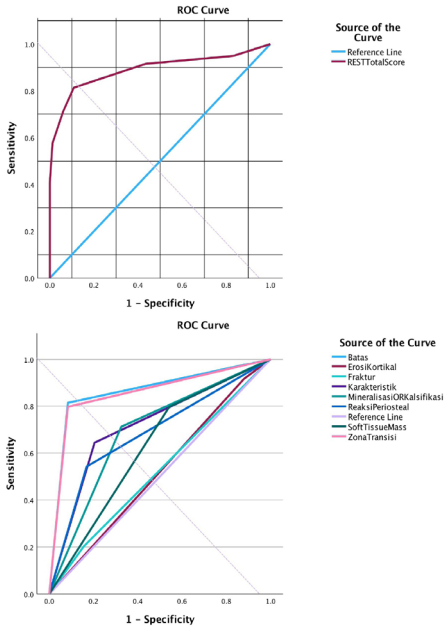

Figure 4: The sensitivity and specificity of REST scoring were plotter on ROC curve + ROC Curve for each scoring criteria

Based on the area under the ROC curve of each criterion, it was found that the criteria of lesion boundary, transition zone, characteristics, and tumor content had higher accuracy (area under ROC curve 0.7 - 0.8) than the criteria of periosteal reaction, connective tissue mass, fracture, and cortical erosion (area under ROC curve 0.5 - 0.6) (Figure 4). A study that conducted a diagnostic test of radiological images (plain radiographs) mentioned that the 4 radiological criteria with the highest positive predictive value were lesion border, transition zone, cortical erosion, and periosteal reaction (13,14). It can be seen that in both the study by Salunke and this current study, the lesion boundary, transition zone, characteristics, and tumor content criteria had higher accuracy than the other criteria.

Diagnosis Accuracy

The diagnosis accuracy of REST scoring is 85.3%. Based on a study conducted by Salunke (2021), the diagnosis accuracy of REST scoring obtained from the formula in section 4.9 is 99%. On the other hand, the diagnosis accuracy of X-ray radiology images for diagnosing bone tumors is 86.95% (14). It can be concluded that both tests have high diagnostic accuracy. However, in the same study, diagnosis using X-ray radiology resulted in a low NPV (negative predictive value) (36.3%) compared to the NPV of REST scoring based on this study (87.1%) which means that out of all negative values, there is a low number of true negatives and high false negatives in the diagnosis of bone tumors with X-ray radiology. This means that negative values of malignancy in X-ray diagnosis have a high probability of being false and misdiagnosis of bone tumors that should be malignant into benign. This is also supported by the low specificity or true negative value of X-ray (44.4%). Model of the REST scoring method shown in Table 2, which is a model for implementing the REST scoring system on two sample X-ray images which provide a Radiological Evaluation Score for Bone Tumors (REST) value 1/8.

Limitations

The current study had few limitations. The limited number and variety of samples that had imaging documentation data meant that researchers could not freely take inclusion samples and made pretty much amount of sample exclusion. This is because most bone tumor patients at the hospital are referral patients who bring physical images, so they are often not recorded in the central medical record system. Other than that, it was a limited time for the researchers to collect radiology documentation data from other data sources. Therefore, not all patients with bone tumors had image documentation data.

Conclusion

In conclusion, the Radiological Evaluation Score for Bone Tumors (REST) REST scoring system offers a structured

methodology for evaluating radiographs of patients with suspected bone tumors, enhancing diagnostic precision and consistency in clinical assessment. This scoring system could help clinicians, starting from general practitioner until radiologist specialist, to giving more objective assessment and prevent misdiagnosis due to lesion mimicking, in combination with clinical evaluation and other investigations including MRI and CT scans. Although gold standard diagnosis of bone tumors is based on histopathological by biopsy, using a structured assessment will help to reduce the chance of missing key features criteria needed for suspecting benign and malignant bone tumor. The rural area, especially in Indonesia, will also benefited to enhance X-ray radiograph as the primary modality. In the future, we can expand or upgrade the criteria of the scoring system, namely 1) the acceleration of tumor size enlargement; and 2) the number of tumor lesions in a single sample. Further study of REST scoring system for secondary or metastatic bone tumors and study of its accuracy in combination with other radiological modalities are necessary to enhance our knowledge.

Acknowledgement and Ethics Approval

This original article was previously submitted as an undergraduate assignment to the Faculty of Medicine and Health Sciences of the first author's home university and was never published. This work is supported by regional hospital of the first author's province as the medical records and patient cases data source. This study was approved under the ethics committee of Faculty of Medicine and Health Sciences of the first author's home university. (Reference Number of Ethic Approval: 0827/KEPK/XI/2023).

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