ORIGINAL ARTICLE

MSH-5: malignant knee tumors timely detection index

MSH-5: índice para la detección oportuna de tumores malignos de rodilla

Gustavo Rivera-Saldívar[1], Rubén Torres-González[2], Alejandra Cario-Méndez[1], Romeo Técualt-Gómez[1], Rubén A. Amaya-Zepeda[1], Armando Alcántara-Corona[1], and Silvestre Fuentes-Figueroa[1]*

[1]Servicio de Tumores Óseos; [2]Coordinación de Educación e Investigación en Salud. Unidad Médica de Alta Especialidad Dr. Victorio de la Fuente Narváez, Instituto Mexicano del Seguro Social, Mexico City, Mexico

Abstract

Background: *Bone neoplasms are usually misdiagnosed causing a delay in their treatment. Bone neoplasms are usually confused with tendinitis, 31% of the cases corresponds to osteosarcomas and in 21% to Ewing's sarcomas.* **Objective:** *To create a clinical-radiographic instrument of high diagnostic suspicion of knee bone neoplasms to prevent a delay in diagnosis.* **Method:** *A clinimetric study (sensitivity, consistency and validity) was performed in the bone tumor service, Hospital de Ortopedia de la Unidad Médica de Alta Especialidad Dr. Victorio de la Fuente Narváez, Instituto Mexicano del Seguro Social, in Mexico City.* **Results:** *Characteristics of 153 patients were collected. For the sensitivity phase, 3 domains (signs, symptoms, and radiology) and 12 items were included. Consistency was evaluated with ICC (0.944), 95%CI (0.865-0.977), $p < 0.001$ and α-Cronbach (0.863). Index obtained a sensitivity of 0.80 and a specificity of 0.882 were obtained. The positive predictive value of the test was 66.6% and the negative predictive value was 93.75%. The positive likelihood ratio was 6.8 and the negative likelihood ratio was 0.2. Validity was evaluated using r-Pearson (0.894; $p < 0.001$).* **Conclusions:** *A high suspicion clinical-radiographic index was designed to detect malignant knee tumors with adequate sensitivity, specificity, appearance, content, criteria, and construct validity.*

Keywords: *Knee. Bone neoplasms. Early diagnosis. Physical Examination. Radiography. Pain.*

Resumen

Antecedentes: *Los tumores óseos suelen ser subdiagnosticados, provocando un retraso en su tratamiento. El diagnóstico erróneo más frecuente es tendinitis, en el cual el 31% corresponden a osteosarcomas y el 21% a sarcomas de Ewing.* **Objetivo:** *Crear un instrumento clínico-radiográfico de alta sospecha diagnóstica de tumores óseos de rodilla.* **Método:** *Se realizó un estudio clinimétrico (sensibilidad, consistencia y validez) en el servicio de tumores óseos del Hospital de Ortopedia de la Unidad Médica de Alta Especialidad Dr. Victorio de la Fuente Narváez, Instituto Mexicano del Seguro Social, en Ciudad de México.* **Resultados:** *El índice se realizó tomando las características de 153 pacientes. Para la fase de sensibilidad se incluyeron tres dominios (signos, síntomas y radiología) y 12 ítems. La consistencia se evaluó con coeficiente de correlación intraclase (0.944), intervalo de confianza del 95% (0.865-0.977), $p < 0.001$ y α de Cronbach (0.863). Se obtuvo una sensibilidad del instrumento de 0.80 y una especificidad de 0.882. El valor predictivo positivo de la prueba fue del 66.6% y el valor predictivo negativo fue de 93.75%. La razón de verosimilitud positiva fue de 6.8 y la razón de verosimilitud negativa fue de 0.2. La validez se evaluó mediante r-Pearson (0.894; $p < 0.001$).* **Conclusiones:** *Se diseñó un índice clínico-radiográfico de alta sospecha para detectar tumores malignos de rodilla con adecuada sensibilidad, especificidad y validez de apariencia, de contenido, de criterio y de constructo.*

Palabras clave: *Rodilla. Tumores óseos. Diagnóstico temprano. Exploración física. Radiografía. Dolor.*

***Correspondence:**
Gustavo Rivera-Saldívar
E-mail: gustavozaldivar@hotmail.com

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Introduction

The proper diagnosis of bone tumors requires close cooperation among orthopedic surgeons, pathologists, and radiologists, and it is often achieved late, thus complicating the entire process of treating the neoplasm[1,2].

The highest incidence rates of osteosarcoma and Ewing's sarcoma occur during the second decade of life, with annual incidences reported of 2 and 0.8 per million inhabitants, respectively[3,4]. Due to their low frequency, bone neoplasms are often overlooked, and their detection is complex[5]. These neoplasms are partially defined in the medical literature available as a set of heterogeneous clinical signs. Whide B et al.[6] describe pain as the initial symptom (often found nonspecifically), associated with exertion, and occasionally with palpable masses. Between 67% and 70% of malignant bone tumors occur in the knee, making it the most widely affected osteoarticular segment of the human skeleton by these conditions[6,7].

Conventionally, the knee presents nonspecific pain that is often managed late. The diagnosis can be delayed up to 3 years after symptom onset[8-10]. Bone metastases are also difficult to evaluate properly, resulting in delayed treatment[11]. Some series report delays of up to 17 weeks from the initial medical consultation to diagnosis[12,13]. Ichinohe et al.[14] found a delay in diagnosis ranging from 3 to 307 days, with diagnostic errors in 56.4% of the patients being reported. Delayed diagnosis and the management of bone tumor lesions are also associated with inadequate plain x-rays, poor radiographic techniques being used, and incomplete initial medical histories[15].

Tumors can be the result of traumatic conditions, thus leading to misdiagnosis or inappropriate invasive diagnostic or therapeutic procedures. Muscolo et al.[16] reported a total of 3.7% of knee arthroscopic procedures resulting from misdiagnosis categorized as sports injuries.

Ewing's sarcoma is often underdiagnosed, mismanaged, and confused with other conditions such as osteomyelitis or fibrous dysplasia[17,18]. Confirmation of the presence of these tumors sometimes requires sophisticated analyses[19].

Chondrosarcoma represents 25% of bone sarcomas and often occurs in adults aged 30 to 60 years. Its categorization is often difficult to achieve, which is essential for proper treatment[20-22]. Overall, prognostic factors for musculoskeletal tumors continue to be poorly understood[23,24].

Another factor identified for delayed diagnosis is the indication, or not, of a plain x-ray (8 vs 19 weeks of diagnostic delay, respectively; $p \leq 0.001$)[6]. According to Aboulafia et al.[25], the indication for often unnecessary studies leading to inconclusive diagnoses was nearly the same between general practitioners and orthopedic surgeons. The most common incorrect diagnosis reported is tendinitis, occurring in 31% of cases when it was actually osteosarcoma, and 21% when it was Ewing's sarcoma. The actual diagnosis is often achieved 6 to 8 months after symptom onset[6].

Following the guidelines drafted by Feinstein[26-28], and Torres-González et al.[29], an assessment tool was developed to enable the early and proper detection of bone tumors by both primary and secondary care physicians.

Method

A clinimetric, prospective, controlled, observational, cross-sectional, and analytical trial was conducted in the Bone Tumors Unit of Hospital de Ortopedia Unidad Médica de Alta Especialidad (UMAE) Dr. Victorio de la Fuente Narváez, Mexican Institute of Social Security (IMSS), in Mexico City, Mexico.

Based on clinimetric analyses[26-29], characteristics were selected to be included in the index to determine its sensitivity, consistency, and validity (Table 1).

Sensitivity phase

The purpose, clinical framework, justification, and clinical applicability were discussed with 4 orthopedic experts with over 15 years of experience. The possibilities for creating the index, its perspectives, and application were identified. Initially, a total of 4 domains (low variability) were projected (signs, symptoms, radiology, and family history). These domains were modified based on their frequency of presentation.

The domains were divided into items, and their association with the diagnosis of malignant knee tumors and biological plausibility for integration into the index was weighed. The symptom domain included characteristics of pain[30,31]. The clinical signs domain included the presence of palpable mass, volume increase, or cutaneous trophic changes. The radiology domain included lesion characteristics on the x-rays (lytic lesion, blastic lesion, or periosteal reaction, location, site). The family history domain and the variables

Table 1. Clinimetric analysis

Sensitivity
– Purpose and frame of reference
– Clinical justification
– Clinical applicability
– Comprehensibility
• Simplicity
• Low variability
• Transparency
• Biological connotation
– Replicability
• Clarity of instructions
• Unbiased examination
– Availability of the output scale
• Comprehension
• Discrimination
– Appearance validity
• Focus on personal exchange
• Focus on basic evidence
• Biological coherence of components
• Personal collaboration
– Content validity
• Significant omissions
• Inappropriate inclusions
• Weighing of components
• Satisfactory elementary scales
• Quality of basic data
• Ease of use
Consistency
– Scientific importance of consistency
– The role of operational instructions and criteria
– The role of pilot studies
– Internal consistency
– Statistical expression of consistency
– External consistency
– Need to conduct field studies to verify variability
Validity
– Criterion validity
– Construct validity

fever and weight loss were excluded due to their low association. The most common items were included in an orderly systematic survey, and an instructional guide for using the index was formulated, which ended the sensitivity phase.

Consistency phase

To analyze the consistency of the index, the survey was applied to patients with knee pain by 2 standardized and blinded observers. The entry symptom was knee pain, and the outcome data were divided into low and high diagnostic suspicion patients. The physicians assigned (2 orthopedic specialists) and previously standardized (reproducibility), applied the index separately on the same day. Feedback was collected from the physicians who applied the index to assess its appearance, content validity, and performance-related issues.

Patients received their subsequent care conventionally to verify the diagnosis through biopsy and, in the case of non-tumoral pathology, Kellgren and Lawrence[32] radiographic criteria for osteoarthritis were used. Patients with knee fractures were not included intentionally.

In case of coexisting osteoarthritic and tumoral pathology, the latter was considered as the output response, being the index output (low and high suspicion) evaluated as usual.

Consistency was evaluated with κ values and intraclass correlation coefficient (ICC) for output data to make the necessary adjustments (calibration) and increase the instrument's sensitivity.

Validity phase

The analysis was performed using the reference method (histopathological) for bone tumors and by construct and convergence for non-tumor diagnoses.

Statistical analysis

The data were collected in a database for analysis (using SPSS Demo version 22.0). For the sensitivity phase, the univariate analysis was conducted, including measures of dispersion and central tendency for quantitative variables. The chi-square test and measures of association with odds ratios (OR) were used to assess the qualitative variables. P values < 0.05 were considered statistically significant. For consistency analysis, the inter-observer variability was measured using κ coefficient for dichotomous variables and weighted κ to study clinical categories inter-observers. ICCs were calculated for the numerical values of the index output score. Cronbach's α was calculated for internal reliability and scale measurement reliability. Sensitivity and specificity analyses, positive and negative predictive values, and positive and negative likelihood ratios were calculated to evaluate the index as a diagnostic test.

The validity analysis was performed using Pearson's correlation coefficient or Spearman's r for continuous numerical values.

Results

A total of 153 patients with knee pain as the presenting symptom were evaluated to build and evaluate the index.

Sensitivity analysis

The characteristics of pain included in the index are shown in table 2. The radiographic characteristics were evaluated in a total of 132 eligible patients, 74 of whom were men and 58, women. The mean age was 26.03 (± 17.7) years. Table 3 shows the radiographic characteristics with the highest weighting. Elements with significant associations were added to the document named MSH-5 (acronym of our hospital unit: Magdalena de las Salinas-Hospital) (Fig. 1).

Consistency analysis

The consistency phase was evaluated in 21 patients with knee pain, 7 of whom were men and 14, women. The κ coefficient found for the sample between the 2 blinded observers under repetition of the index in the same patient was 0.741 ($p < 0.001$). The proportional disagreement of all observations ([observer A value-observer B value]/[observer A value + observerB value/2]) was 16%.

The chi-square test for the output variables under low and high-risk compared against the presence or absence of neoplasm was statistically significant, with p values < 0.001 and 0.003 for observer A and observer B, respectively. Regarding the output variables (high and low risk of neoplasm), concordance measured through Cronbach's α coefficient was 0.863. The ICC value was obtained for numerical variables using a 2-factor random effects model. It was calculated for the raw numerical output data of the index without categorization, for both the overall score and the score for each domain (signs, symptoms, and radiology). Table 4 summarizes the results of the different ICC values evaluated for the index. Regarding the analysis for diagnostic test validation, sensitivity and specificity rates of 80% and 88.2%, respectively, were obtained. The positive and negative predictive values were 66.6% and 93.75%, respectively. The positive and negative likelihood ratios were 6.8 and 0.2, respectively.

Validity analysis

The correlation values for the sign and radiology domains (Spearman's r) were r = 0.533 and r = 0.989, respectively (p = 0.013, and p < 0.001).

The correlation values for the symptom domain and the overall score (Pearson's r) were r = 0.982 and r = 0.894, respectively (both p < 0.001).

Table 2. Characteristics of pain in patients with oncological and non-oncological pathology

	p*	OR	95%CI
Age			
< 20 years	< 0.001	64.4	(14.5-284)
> 20 years			
Duration	< 0.001	7.26	(3.34-15.7)
0-4 months			
> 4 months			
Intensity			
Mild	0.26	0.44	(0.13-1.43)
Moderate	< 0.001	0.11	(0.05-0.23)
Severe	< 0.001	5.7	(2.82-11.64)
Frequency			
Constant	0.01	2.8	(1.33-6.13)
> 2 episodes/day	0.006	0.3	(0.18-0.72)
> 2 episodes/week	0.12	0.55	(0.27-1.09)
Predominio			
Nocturnal	< 0.001	7.44	(3.1-17.8)
Diurnal			

95%CI: 95% confidence interval; OR: odds ratio.
*Chi-square test (tetra, or multitetrachoric).
Taken of reference 30.

Table 3. Association between radiographic characteristics and malignant lesions

Caracteristic (n = 132)	p*	OR	95% CI	Power
Lytic				
Active	< 0.001	26.85	2.83-16.85	> 80
Aggressive	< 0.001		3.21-224	> 80
Blastic				
Extraosseous cartilaginous	< 0.001	0.04	0.006-0.37	> 80
Intraosseous poorly defined	< 0.001	36.15	4.4-295	> 80
Extraosseous poorly defined	0.37	5.52	0.48-62.95	> 80
Periosteal reaction				
Codman	< 0.001	31.66	3.84-261	> 80
Sunburst	< 0.001	36.15	4.4-295	> 80
Location				
Central	0.009	3.03	1.37-6.69	> 80
Destructive pattern				
Moth-eaten:	< 0.001	22.93	2.7-194	> 80
Permeative	0.02	11.75	1.2-109	> 80

IC95%: 95% confidence interval; OR: odds ratio.
*Chi-square test (tetra, or multitetrachoric).

Figure 2 illustrates the dispersion of the correlation for the output scores inter-observers and their 95% confidence interval.

Discussion

The MSH-5 index has no similar precedent in the clinical or clinimetric field. It arises from the need to

Name: _____ NSS: _____

Age: _____ ID: _____

MSH-5 index

Age	
> 20 years	1
≤ 20 years	2
Signs:	
Negative	0
Visible mass or increased volume	4
Skin is stretched and with collateral venous network	5
Radiology:	
Active or aggressive lytic lesion	5
Poorly defined intraosseous blastic lesions reaction	5
Periosteal reaction (Codman, sun-ray type, or laminar)	5
Central location	3
Moth-eaten or permeative pattern	2
Symptoms: PAIN	
Duration > 4 months	0
Duration < 4 months	3
Constant pain	1
Constant pain	1
(Apply VAS): intense pain	2
Worse at night, wakes you up or prevents you from sleeping	2
TOTAL	

No pain	Maximum pain
0	10

Maximum pain

≤ 12: low risk of neoplasm
> 12: high risk of neoplasm

Figure 1. *Integrated scale with the highest-weighted elements (MSH-5). Detailed instructions for the application of this index can be requested to the lead author via e-mail.*

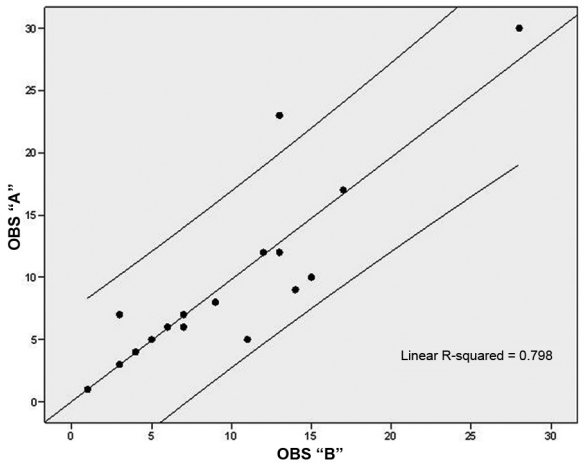

Figure 2. *Pearson's correlation coefficient scatter plot of inter-observer scores. OBS "A", observer A; OBS "B", observer B; linear R-squared: coefficient of determination.*

Table 4. Intraclass correlation coefficients for numeric variables of overall score and by domains

Domain	ICC	95%CI	p
Signs	0.696	0.250 0.877	0.005
Symptoms	0.990	0.976 0.996	< 0.001
Radiology	0.961	0.904 0.984	< 0.001
Total	0.944	0.865 0.977	< 0.001

ICC: intraclass correlation coefficient, calculated using the 2-factor random effects model; 95%CI: 95% confidence interval.
$\alpha = 0.05$.

promote timely diagnosis by grouping the most important characteristics of knee tumor pathology and formulating a high diagnostic suspicion in a simple

manner. It is named after the acronym of our hospital unit (Magdalena de las Salinas-Hospital) and is the 5th of other clinimetric elements created within it.

Clinical presentation is a key element for the diagnosis of primary and metastatic bone tumors, along with radiology, while pain is the most common finding in oncological patholog.[1,6,16,17,23,25,33,34]. The index was systematically planned and developed from scratch by compiling clinical and radiographic characteristics into a summarized and organized tool. During the sensitivity phase, a total of 293 patients were included, and the characteristics of pain, frequency of clinical signs, radiographic characteristics, and hereditary family history were studied. The index was built with data obtained from these patients. The ORs < 1 (protective) were excluded from the index due to their low variability. The index final variables (Fig. 1) are related to clinical data found in the medical literature available[2,12,35]. The inter-observer agreement obtained was "very good" according to the Landis and Koch guidelines[36]. The Cronbach's α coefficient for the output data (high and low suspicion of malignant tumor) is acceptable and non-redundant[37]. With the data obtained from the patients and the ICC, a proper consistency among the index components was seen.

The index evaluated as a diagnostic test achieved acceptable sensitivity and specificity rates. The likelihood ratios considered important are those with values > 10. In our series, the positive likelihood ratio indicates a good ability to detect positive patients, while a negative likelihood ratio of 0 is indicative of an excellent ability to exclude the disease in the absence of it.

The delay in the diagnosis of bone tumors will always act to the patient's prognostic detriment[2,12,13,34,38,39]. The creation of this tool aims to be useful in reversing such delays and preventing related human consequences (physical, emotional, and social)[40]. Our group does not support the need for a larger-scale field study, at this moment, as it is deemed unproductive in terms of information for index construction. The index is ready to be used to assess all these application parameters.

Conclusions

Based on the resources from UMAE Dr. Victorio de la Fuente, including its expert staff and patients, we could create a clinical-radiographic index for the timely detection of musculoskeletal knee tumors. This index has adequate sensitivity and specificity rates, correct positive and negative predictive values, and proper positive and negative likelihood ratios. The MSH-5 index has proper sensitivity and specificity rates, proper positive and negative predictive values, and positive and negative verisimilitude ratios.

Funding

The project was funded exclusively with the researchers' resources.

Conflicts of interest

None whatsoever.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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