

## **Bone tumors of the foot and ankle - A protocol for systematic review**

**Tumores ósseos do pé e tornozelo - Um protocolo para revisão sistemática**

**Tumores ósseos del pie y el tobillo - Un protocolo para la revisión sistemática**

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### **Abstract**

Bone tumors arising from the foot and ankle are relatively rare. The correct diagnosis is commonly ignored, and the potential risk of these tumors is often underestimated. Due to the rarity and particularities of the presentation, there is a lack of evidence on epidemiological data related to the distribution of bone tumors of the foot and ankle by age group, gender and location. As far as we know, no systematic review or meta-analysis was performed on the grouping of bone tumors in this region. The objective of this protocol is to design a systematic review of the evidence to verify these data. Systematic literature research will be carried out in the PubMed/MEDLINE, Embase (by CAPES JOURNALS) and LILACS databases, without time and linguistic restrictions in the search strategy. The reference lists of the included articles will be evaluated to detect unidentified studies. Two evaluators will independently select the articles, extract the data and assess the risk of bias in the selected studies. If applicable, meta-analysis will be carried out, extracting data for the number of events and total patients to perform proportion meta-analysis using the R software, with the "meta" package (version 4.9–6), the "metaprop function" for aspect ratio data. The results of this review will be added to the existing literature, providing convincing information on the epidemiology of these neoplasms, important data that will support future research and help in possible diagnostic, preventive and therapeutic measures. This protocol will provide a reliable theoretical basis for the research that will follow.

**Keywords:** Ankle; Bone and bones; Bone neoplasms; Epidemiology; Foot; Systematic review.

### **Resumo**

Tumores ósseos que surgem a partir do pé e tornozelo são relativamente raros. O diagnóstico correto é comumente ignorado, e o risco potencial desses tumores é frequentemente subestimado. Devido à raridade e particularidades da apresentação, faltam evidências sobre dados epidemiológicos relacionados à distribuição dos tumores ósseos de pé e tornozelo por faixa etária, sexo e localização. Até onde sabemos, nenhuma revisão sistemática ou meta-análise foi realizada sobre o agrupamento de tumores ósseos nesta região. O objetivo deste protocolo é projetar uma revisão sistemática de evidências para verificar estes dados. Será realizada pesquisa sistemática da literatura nos bancos de dados PubMed/MEDLINE, Embase (por PERIÓDICOS CAPES) e LILACS, sem restrições temporais e linguísticas na estratégia de busca. As listas de referência dos artigos incluídos serão avaliadas para detectar estudos não identificados. Dois avaliadores selecionarão independentemente os artigos, extrairão os dados e avaliarão o risco de

viés nos estudos selecionados. Caso aplicável, será realizada metanálise, extraindo dados para o número de eventos e pacientes totais para realizar a metanálise proporcional utilizando o software R, com o pacote "meta" (versão 4.9-6), a "função metaprop" para dados de proporção. Os resultados desta revisão se somarão à literatura existente, fornecendo informações convincentes sobre a epidemiologia dessas neoplasias, dados importantes que apoiarão pesquisas futuras e auxiliarão em possíveis medidas diagnósticas, preventivas e terapêuticas. Este protocolo fornecerá uma base teórica confiável para a pesquisa que se seguirá.

**Palavras-chave:** Tornozelo; Osso e ossos; Neoplasias ósseas; Epidemiologia; Pé; Revisão sistemática.

### Resumen

Los tumores óseos que surgen del pie y el tobillo son relativamente raros. El diagnóstico correcto se ignora comúnmente, y el riesgo potencial de estos tumores a menudo se subestima. Debido a la rareza y particularidades de la presentación, existe una falta de evidencia sobre los datos epidemiológicos relacionados con la distribución de los tumores óseos del pie y el tobillo por grupo de edad, sexo y ubicación. Hasta donde sabemos, no se realizó ninguna revisión sistemática o metanálisis sobre la agrupación de tumores óseos en esta región. El objetivo de este protocolo es diseñar una revisión sistemática de las evidencias para verificar estos datos. La investigación sistemática de la literatura se llevará a cabo en las bases de datos PubMed/MEDLINE, Embase (por CAPES JOURNALS) y LILACS, sin restricciones de tiempo y lingüísticas en la estrategia de búsqueda. Se evaluarán las listas de referencias de los artículos incluidos para detectar estudios no identificados. Dos evaluadores seleccionarán de forma independiente los artículos, extraerán los datos y evaluará el riesgo de sesgo en los estudios seleccionados. En su caso, se llevará a cabo un metanálisis, extrayendo datos para el número de eventos y el total de pacientes para realizar un metaanálisis de proporción utilizando el software R, con el paquete "meta" (versión 4.9-6), la "función metaprop" para los datos de relación de aspecto. Los resultados de esta revisión se sumarán a la literatura existente, proporcionando información convincente sobre la epidemiología de estas neoplasias, datos importantes que apoyarán futuras investigaciones y ayudarán en posibles medidas diagnósticas, preventivas y terapéuticas. Este protocolo proporcionará una base teórica confiable para la investigación que seguirá.

**Palabras clave:** Tobillo; Huesos; Neoplasias óseas; Epidemiología; Pie; Revisión sistemática.

## 1. Introduction

Bone tumors that arise in the foot and ankle are relatively rare (Ozdemir et al., 1997; Chou et al., 2009; Hofstaetter et al., 2010; Azevedo et al., 2013; Özer et al., 2017, Ebeid et al., 2019), accounting for approximately 1-2% of all bone tumors (Özer et al., 2017). However, considering that this appendicular segment corresponds to only 3% of the body mass, it can be deduced that the incidence of foot and ankle bone neoplasms is proportionally higher than that observed in the rest of the musculoskeletal system (Toepfer, 2017; Toepfer et al., 2018). In this location, soft tissue neoplasms are more prevalent than bone lesions at a ratio of 10:1, and benign lesions are at least four times more common than malignant lesions (Ozdemir et al., 1997; Kilgore & Parrish, 2005; Azevedo et al., 2013); the latter corresponds to less than 2% of all sarcomas and less than 10% of soft tissue sarcomas (Azevedo et al., 2013). It is important to mention that these data represent only surgically treated tumors, therefore the actual incidence of these lesions remains unknown (Toepfer, 2017; Toepfer et al., 2018).

The foot has relatively thin musculature and subcutaneous tissue, making it relatively easy to inspect and palpate tumors in this topography (Ozdemir et al., 1997; Chou et al., 2009; Özer et al., 2017; Toepfer, 2017). Additionally, it consists of multiple small joints, allowing early detection of pain and functional disorders, making clinically evident even small tumors (Özer et al., 2017). Rarely, a mass remains unnoticed for a long time (Ozdemir et al., 1997). Despite this, the correct diagnosis is commonly ignored, and its potential risk is usually underestimated; errors or delays in the diagnosis of tumors located in the foot and ankle may result in inadequate resection and/or a higher recurrence rate (Ozdemir et al., 1997; Thacker et al., 2008; Chou et al., 2009; Azevedo et al., 2013; Ruggieri et al., 2014; Mascard et al., 2017; Özer et al., 2017; Toepfer, 2017).

Bone tumors located in the foot and ankle occurs in all age groups. Benign neoplasms occur more frequently from the third to the fourth decade of life, while malignant lesions are more common from the fourth to the sixth decade, a period in which metastatic lesions and soft tissue sarcomas are more frequent (Özer et al., 2017).

Gender does not show a significant correlation with diagnosis in most studies; however, benign lesions appear more frequently in women and malignant lesions occur more commonly in men, as in cases of Ewing's sarcoma and osteosarcoma,

the most common malignant foot and ankle bone neoplasms (Özer et al., 2017).

Regarding location, the classification of Ruggieri et al. (2014), adapted by Toepfer et al. (2018), distributes bone tumors in anatomical areas: forefoot, middle foot, hindfoot, and ankle. In their series composed of 409 patients (413 feet), Toepfer et al. (2018) found that 30% of tumors were in the hindfoot, 28.6% in the ankle, 21.5% in the midfoot, and 19.9% in the forefoot, with laterality to the right in 54.2%, to the left in 44.8%, and bilaterality in 1% of cases. Other authors also point hindfoot as the most common bone tumor location, reaching up to 51.6% of the total lesions, with the calcaneus being the most frequently affected bone (Ozdemir et al., 1997).

Any bone neoplasm, whether benign, malignant, or metastatic, can be located on the foot and ankle.

The occurrence of sarcomas is notoriously difficult to differentiate from benign lesions on clinical and radiographic examination (Toepfer et al., 2018). This difficulty, along with its relative rarity, often leads to inadequate treatment of foot and ankle primary malignant bone neoplasms (Mascard et al., 2017) - mistaken clinical diagnoses often occur (Ozdemir et al., 1997; Özer et al., 2017). Metastatic lesions (acrometastases) are rare, ranging from 0.01% to 1.3% (Chou et al., 2009).

Treatment of foot and ankle tumors varies according to histological type, clinical behavior and location of lesions.

Benign tumors or tumor-like conditions are usually followed by observation (latent lesions) or treated by intralesional resection associated with local adjuvance (with or without filling with bone grafts, bone substitutes, or polymethylmethacrylate), marginal or wide resection.

Since a diagnosis of primary malignant tumor of foot and ankle is reached, it is important to define about the possibility of preservation of the affected limb (Özger et al., 2018, Foo & Raby, 2005). The classic treatment for malignant conditions of the foot and ankle is below-knee amputation at different levels - with the advancement of diagnostic technologies and adjuvant therapies, it is now possible to benefit patients with limb-salvage operations or partial amputations (Chou et al., 2009), even in cases with late diagnosis or previous inappropriate treatment (Özger et al., 2018). The limb salvage surgery aims to achieve local control of the tumor through wide resection margins, maintaining a plantigrade foot, with preserved sensitivity and satisfactory function; marginal excision may result in inadequate local control with a high rate of local recurrence, while wide or radical resection may compromise function - when this balance cannot be achieved, amputation is indicated (Ebeid et al., 2019). Patients with suspected foot and ankle bone sarcomas should be referred to orthopedic oncology referral centers, where diagnostic and/or therapeutic errors are less common (Thacker et al., 2008). The orthopedic surgeon involved in the treatment should be familiar with the diagnostic and staging criteria (Guedes et al., 2010, Guedes, Oliveira, Costa, et al., 2021, Guedes, Oliveira, de Melo, et al., 2021) as well as therapeutic options, as each tumor may vary in its clinical presentation (Toepfer et al., 2018).

Small death rates (2.1%) were associated with foot and ankle tumors (Chou et al., 2009). The survival rate for malignant lesions ranged from 40% to 70% (Chou et al., 2009; Azevedo et al., 2013).

Due to the rarity and particular characteristics of the presentation, there is a lack of evidence regarding the distribution of foot and ankle bone tumors by age group, gender, and location. This systematic review protocol was designed to comprehensively contribute to the literature on epidemiological data that is not yet well established.

## **2. Methodology**

### **2.1 Protocol register**

This systematic review protocol was drafted under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA) (Moher et al., 2010; Page et al., 2021). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the record CRD42021281687.

## **2.2 Ethics**

Ethical approval will not be necessary for this systematic review, and the meta-analysis will not contain any private information on participants or violate their human rights.

## **2.3 Criteria for the included studies in the review**

**2.3.1 Types of studies:** Case reports with  $\geq 20$  patients, including case series and observational analyses. Studies published in English, Portuguese, and Spanish will be included.

**2.3.2 Inclusion criteria:** Studies that have evaluated individuals with foot and ankle bone tumors, regardless of age, gender, and ethnicity.

## **2.4 Search strategy**

A systematic literature search will be carried out in the PubMed/MEDLINE, Embase (using Periódicos CAPES), and LILACS databases without temporal and language restrictions in the search strategy. In the bibliographic survey, the use of MeSH-controlled vocabulary and free terms will be adopted, being grouped and/or crossed with the Boolean operators "OR" and "AND", as shown in **Table 1**. The reference lists of the included articles were evaluated to identify unidentified studies.

## **2.5 Data screening and extraction**

One of the researchers will conduct the search through the databases and export the results to the web domain selection management program Rayyan: Rayyan Qatar Computing Research Institute (Rayyan QCRI) and remove duplicates. After that, two evaluators will independently select the articles by titles and abstracts, identifying eligible studies for full reading. All study selection procedures were based on PRISMA flowchart (**Figure 1**). In cases of divergence, the evaluators will discuss about the inclusion. If no agreement is achieved, a third evaluator will be requested to make the tiebreak.

The data will be extracted using Microsoft® Excel® (Microsoft Corporation, 2019). To avoid bias in the extraction process, two evaluators independently will perform the extractions. Information on the selected studies, characteristics of the population evaluated, and diseases studied will be extracted.

### **2.5.1 Dealing with missing data**

If the data of potential studies are missing, insufficient, or vague, we will attempt to contact the corresponding authors to retrieve the necessary data via email. Studies will be excluded if relevant data could not be obtained using the approach.

## **2.6 Risk of bias (quality) assessment**

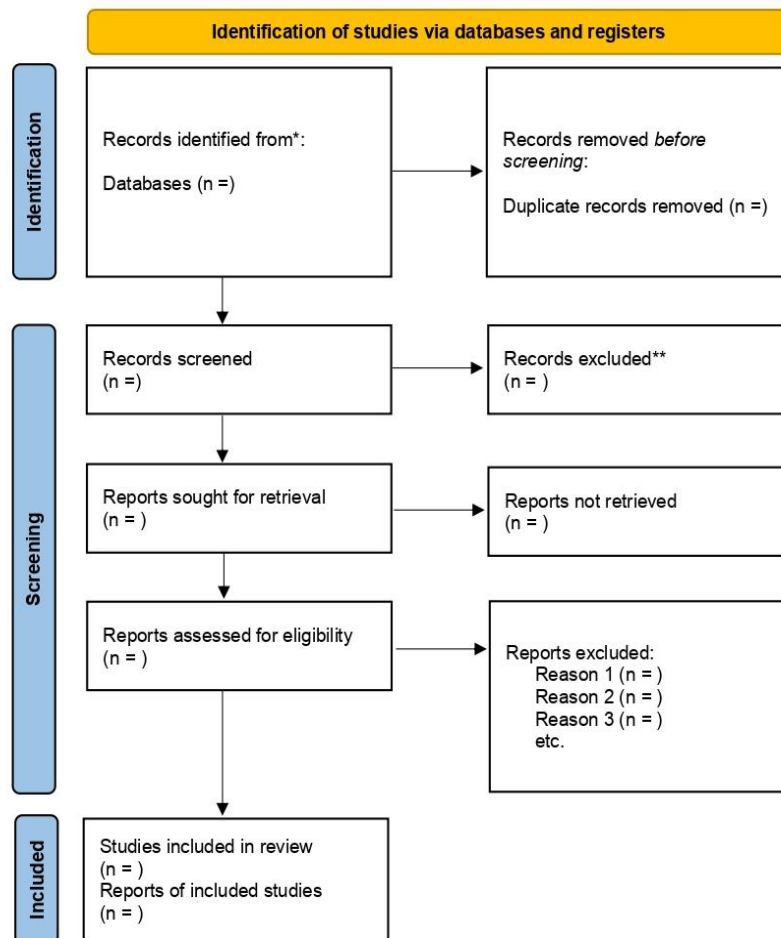
Two evaluators independently will assess the risk of bias in the selected studies by using the tool proposed by Murad et al. (2018) developed to assess the Methodological Quality and Case Series Synthesis and Case Report Protocol, an instrument derived from the Scale from Newcastle – Ottawa (NOS), except for two questions not relevant to our review ("Was there a challenge/re-challenge phenomenon?" and "Was there a dose-response effect?").

**Table 1.** Database search strategy.

	<b>PubMed</b>	<b>Embase</b>	<b>LILACS</b>
#1	"Foot Bones"[Mesh]	mh:"Foot Bones"	mh:"Foot Bones"
#2	"Metatarsal Bones"[Mesh]	mh:"Metatarsal Bones"	mh:"Metatarsal Bones"
#3	Metatars*[title/abstract]	Metatars\$	Metatars\$
#4	"Tarsal Bones"[Mesh]	mh:"Tarsal Bone"	mh:"Tarsal Bone"
#5	"Cuneiform Bone"[Title/Abstract]	"Cuneiform Bone"	"Cuneiform Bone"
#6	"Cuboid Bone"[Title/Abstract]	"Cuboid Bone"	"Cuboid Bone"
#7	"Tarsal Bones/anatomy and histology"[Mesh]	mh:"Tarsal Bones/AH"	mh:"Tarsal Bones/AH"
#8	"Calcaneus"[Mesh]	mh:"Calcaneus"	mh:"Calcaneus"
#9	"Heel Bone"[Title/Abstract]	"Heel Bone"	"Heel Bone"
#10	"Calcaneus/anatomy and histology"[Mesh]	mh:"Calcaneus/AH"	mh:"Calcaneus/AH"
#11	"Talus"[Mesh]	mh:"Talus"	mh:"Talus"
#12	"Toe Phalanges"[Mesh]	mh:"Toe Phalanges"	mh:"Toe Phalanges"
#13	"Toe Phalanges/anatomy and histology"[Mesh]	mh:"Toe Phalanges/AH"	mh:"Toe Phalanges/AH"
#14	"Ankle"[Mesh]	mh:"Ankle"	mh:"Ankle"
#15	"Hallux"[Mesh]	mh:"Hallux"	mh:"Hallux"
#16	<b>#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15</b>	<b>#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15</b>	<b>#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15</b>
#17	"Neoplasms"[Mesh]	mh:"Neoplasms"	mh:"Neoplasms"
#18	Neoplasm*[Title/Abstract]	Neoplasm\$	Neoplasm\$
#19	"Bone Neoplasms"[Mesh]	mh:"Bone Neoplasms"	mh:"Bone Neoplasms"
#20	Tumor*[Title/Abstract]	Tumor\$	Tumor\$
#21	Malignan*[Title/Abstract]	Malignan\$	Malignan\$
#22	Benign Neoplasm*[Title/Abstract]	Benign Neoplasm\$	Benign Neoplasm\$
#23	"Bone Cancer"[Title/Abstract]	"Bone Cancer"	"Bone Cancer"
#24	<b>#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23</b>	<b>#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23</b>	<b>#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23</b>
#25	<b>#16 AND #24</b>	<b>#16 AND 24</b>	<b>#16 AND 24</b>

Source: Authors.

**Figure 1.** The research flowchart.



Source: Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A. e Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed.)*, 372, n71. <https://doi.org/10.1136/bmj.n71>

## 2.7 Statistical analysis

### 2.7.1 Data analysis and processing

Quantitative synthesis was performed if the included studies were homogeneous. Homogeneity will be evaluated in a manner like that of the study design, population, and statistics reported in previous studies. We will conduct a narrative synthesis of the results of the included studies, structured around the types of bone tumors in the ankle and foot, in addition to the anatomical and histological characteristics of the tumor, patient characteristics, gender, and age.

If appropriate, meta-analyses will be conducted, extracting data for the number of events and total patients to perform proportion meta-analysis using the R software, with the "meta" package (version 4.9–6), the "metaprop function" for aspect ratio data. We present the combined results of proportions with their respective 95% confidence intervals using the inverse variance method with a random-effects model using the DerSimonian-Laird estimator for Tau<sup>2</sup>. The data will be adjusted by the Freeman–Tukey double arc transformation, and the confidence intervals will be calculated using the Clopper–Pearson method for individual studies.

### 2.7.2 Analysis of subgroups or subsets

We will perform a subgroup analysis structured around the histologic types of foot and ankle bone tumors, in addition to the anatomical distribution, histological diagnosis of the tumor and patient characteristics, like gender, and age.

## 3. Results and Discussion

We plan to further present the results in a final systematic review as described above in the Methodology section.

### 3.1 Why it is Important to do this Review

The scientific literature about the epidemiological aspects of bone tumors that affect the foot and ankle has not yet been widely investigated. To the best of our knowledge, no systematic review or meta-analysis has been conducted in this context.

The purpose of this protocol is to design a systematic review of level I evidence to ascertain the data.

This work will bring the benefit of informing about the epidemiology of bone tumors that affect the foot and ankle, providing important data that will support future research and assist in possible diagnostic, preventive, and therapeutic measures.

## 4. Final Considerations

This systematic review protocol was designed to comprehensively contribute to the literature on epidemiological data that is not yet well established concerning the distribution of foot and ankle bone tumors by age group, gender, and location. We plan to identify, critically appraise, summarize and provide the certainty about the best, currently available evidence on the subject in question.

The study findings will be published in the form of a dissertation and a systematic review. This work is linked to the master's degree of Fernando Delmonte Moreira (Pos-Graduate Program of the Medical Sciences Medicine Faculty of Santa Casa de Misericórdia de São Paulo, under the orientation supervision of Claudio Santili, MD, PhD (Advisor), and Alex Guedes, MD, MSc, PhD (Co-Advisor) with a scientific, economic, and social impact.

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