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Diagnostic imaging methods used for early and late diagnosis of Neurogenic Heterotopic Ossification.

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Viviana Elizabeth Orbe Montenegro

Jonathan Raymond Guillemot. Director del Instituto de Investigación en Salud y Nutrición (ISYN), Profesor. Director de Trabajo de Titulación

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Diagnostic imaging methods used for early and late diagnosis of Neurogenic Heterotopic Ossification.

Viviana Elizabeth Orbe Montenegro

Nombre del Director del Programa:	Verónica Espinoza Arregui.
Título académico:	Directora Especialización en Imagenología
Director del programa de:	Especialización en Imagenología.

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Decano del Colegio:	Escuela de Especialidades Médicas

Nombre del Decano del Colegio de Posgrados:	Hugo Burgos Yánez
Título académico:	Decano Colegio de Posgrados.

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Nombre del estudiante:	Viviana Elizabeth Orbe Montenegro
Código de estudiante:	00213381
C.I.:	0603551557
Lugar y fecha:	Quito, 1 de septiembre de 2022.

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DEDICATORIA

Dedico este trabajo a mis padres por haberme forjado como la persona que soy en la actualidad, muchos de mis éxitos se los debo a ustedes, entre los que se incluye este. Me formaron con valores y principios que me impulsaron y motivaron constantemente para alcanzar mis anhelos.

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RESUMEN

ANTECEDENTES: La osificación heterotópica (HO), generalmente denominada miositis osificante traumática, paraosteoartropatía o fibromiopatía osificante neurogénica, es la entidad que define el proceso biológico de formación anormal del hueso lamelar maduro dentro de los tejidos blandos extraesqueléticos donde el hueso normalmente no existe. . La incidencia de HO después de una lesión traumática del sistema nervioso central o una lesión de la médula espinal es de alrededor del 10 al 20%.

OBJETIVO: Identificar los métodos de diagnóstico por imagen más utilizados para el diagnóstico precoz y tardío de la osificación heterotópica neurogénica que se presenta en pacientes parapléjicos con trauma neurológico. MÉTODOS: Se realizó una revisión sistemática de la literatura. RESULTADOS: Veintisiete artículos fueron identificados con una población predominantemente masculina. En la mayoría de los artículos seleccionados (18/27 estudios) el método radiológico preferido utilizado para el diagnóstico de la osificación heterotópica neurogénica temprana fue la tomografía, seguida de radiografía y resonancia magnética; aunque tardíamente se utilizaron radiografía, tomografía y resonancia magnética sin diferencias entre ellas. También se utilizó la tomografía 3D para la planificación quirúrgica. En dos estudios se utilizó gammagrafía y SPECT/TC para la evaluación de HO en pacientes entre 16 y 75 años. La mayoría de los pacientes tenían lesión cerebral o de la médula espinal con un intervalo de tiempo de 8 a 295 días desde la lesión inicial hasta el desarrollo de HO. El sitio anatómico evaluado con mayor frecuencia fue la articulación de la cadera.

Palabras clave: osificación heterotópica (HO), radiografía, TC, RM.

ABSTRACT

BACKGROUND: Heterotopic ossification (HO), usually referred to as myositis ossificans traumatica, paraosteoarthropathy or neurogenic ossifying fibromyopathy, is the entity that defines the biological process of abnormal formation of the mature lamellar bone within extra-skeletal soft tissues where bone does not normally exist. The incidence of HO after traumatic central nervous system injury or spinal cord injury is around 10 to 20%.

OBJECTIVE: To identify the most used diagnostic imaging methods for early and late diagnosis of neurogenic heterotopic ossification that is present in paraplegic patients with neurological trauma. METHODS: A literature systematic review was performed. RESULTS: Twenty-seven articles were identified with a predominantly male population. In most of the selected articles (18/27 studies) the preferred radiological method used for the diagnosis of early neurogenic heterotopic ossification was tomography which was followed by radiography and magnetic resonance imaging; although late radiography, tomography and magnetic resonance imaging were used without differences between them. 3D tomography was also used for surgical planning. In two studies, scintigraphy and SPECT/CT were used for the assessment of HO in patients between 16 and 75 years of age. Most patients had brain or spinal cord injury with a time interval of 8 to 295 days since the initial injury to the development of HO. The anatomical site most often evaluated was the hip joint.

Key words: heterotopic ossification (HO), X-ray, CT, MRI.

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INTRODUCTION

Heterotopic ossification (HO), also known as myositis ossificans traumatica, paraosteoarthropathy or neurogenic ossifying fibromyopathy, is the entity that defines the biological process of abnormal formation of the mature lamellar bone within the extra-skeletal soft tissues where bone does not normally exist [1].

In 1918, during World War I, soldiers were found to have paraplegia due to intramedullary gunshot wounds [2]. This entity was known as paraosteoarthropathy [1] which later would correspond to the current term heterotopic ossification (HO). Its meaning depends on the clinical context, the location of the lesions, and whether the lesions are progressive or of isolated appearance. This entity is subdivided into two main types: acquired and genetic; the acquired type being the most predominant. This acquired form is closely related to tissue trauma and it can be observed after joint surgery, musculoskeletal trauma, central nervous system and/or spinal cord injury [3].

HO that occurs due to traumatic head injury and/or spinal cord injury is now defined as neurogenic HO, which represents an increase in morbidity and significant impairment of the quality of life [4]. The etiology is not certainly known; however, recent research has shown a complex interaction between local and systemic factors that includes neuroendocrine, genetic and extrinsic factors [5]. These factors still represent a great challenge for its early diagnosis and respective prophylactic treatment that could significantly reduce disability and additional

medical complications. It occurs predominantly in males without a clear or exact mechanism for its influence. [6–8]

The incidence of HO after traumatic central nervous system injury or spinal cord injury is around 10 to 20% [4]. It is known that as the severity of the lesion increases, the incidence and volume of HO increases [5] and, if additional trauma to the hip is added, the risk of developing HO increases even more. Other risk factors associated to the clinical conditions presented by patients have also been identified such as: severe spasticity, cognitive impairment, prolonged immobilization, deep vein thrombosis, hypercalcemia, tracheotomy, pneumonia and/or urinary tract infections. [9]

Initially, the diagnostic method for this pathology was radiography since this was the only method available. With this method, a diagnosis of the pathology was achieved approximately 6 weeks after the onset of the pathology. Hence, the appearance of tomography helped in the diagnosis of HO [10,11].

As described above and due to the characteristics of this pathology, the diagnosis is radiological, so it presents an early detection. Therefore, in this review, we seek to compare the clinical findings according to their time of appearance (earliest or latest) of heterotopic ossification that occurs in paraplegic patients after neurological trauma.

METHODS

A systematic review of the literature was conducted. The PICOS (Population, Intervention, Comparator, Outcomes and Study type) question was used to formulate the research question (table 1). The bibliographic databases Scopus via Scopus (table 2) were used to select the articles.

Table 1 PICOS framework

Caption: This table describes the systematic review's research question according to the PICOS framework

Item	Definition
Population	Neurogenic heterotopic ossification, neurological trauma.
Interventions	RX, CT, RM.
Comparators	Any.
Outcomes	Etiology of neurogenic heterotopic ossification in patients with neurological trauma. Efficacy of imaging methods in the diagnosis of neurogenic heterotopic ossification.
Study Type	Any type.

Table 2. Search terms Scopus

Caption: This table reports the search terms used for the identification of relevant citations on SCOPUS platform

SEARCH DATE: 23/02/2022		**SCOPUS**	
Items	*#*	*Search terms*	*Number of citations*
Population_Population_OHN	#1	TITLE-ABS-KEY (ossif* OR acvr1 OR "stone man" OR FOP)	
Population_TN	#2	TITLE-ABS-KEY (((spin* OR colum* OR vertebr*) AND (cord* OR cord) AND (injur* OR lesio* OR traum* OR contusi*)) OR (myelopath* AND (injur* OR lesio* OR traum* OR contusi*)))	
Outcome_tomography	#3	TITLE-ABS-KEY (Tomograph* OR Resonanc*)	
Total	#4	#1 AND #2 AND #3	654

In a first phase, exclusion criteria were established for the review of titles and abstracts (table 3). In a second phase, a complete review of the articles was executed where the chosen articles were established. Information was extracted from each selected article in an Excel table.

Table 3. Eligibility criteria
Caption: This table reports the eligibility criteria for the selection of citations during the screening and full-text review, organized by order and category.

Order	Category	Exclusion criteria
1	Duplicates	Duplicates
2	Nature of study	Not study type of interest
		Not human
3	Population	Not pediatric population
4	Population Not OHN or TN patients	Not OHN or TN patients
5	Outcomes Imaging findings	Not including a multidetector CT, MRI, X-ray

RESULTS

The search for articles was made on February 23, 2022, where 27 studies were included (Table 4) out of a total of 879 articles. Details of this process are found in Figure PRISMA.

Most of the studies were observational (25 studies) and mainly retrospective such as Arduini et al [12].

Figure 1. PRISMA Diagram

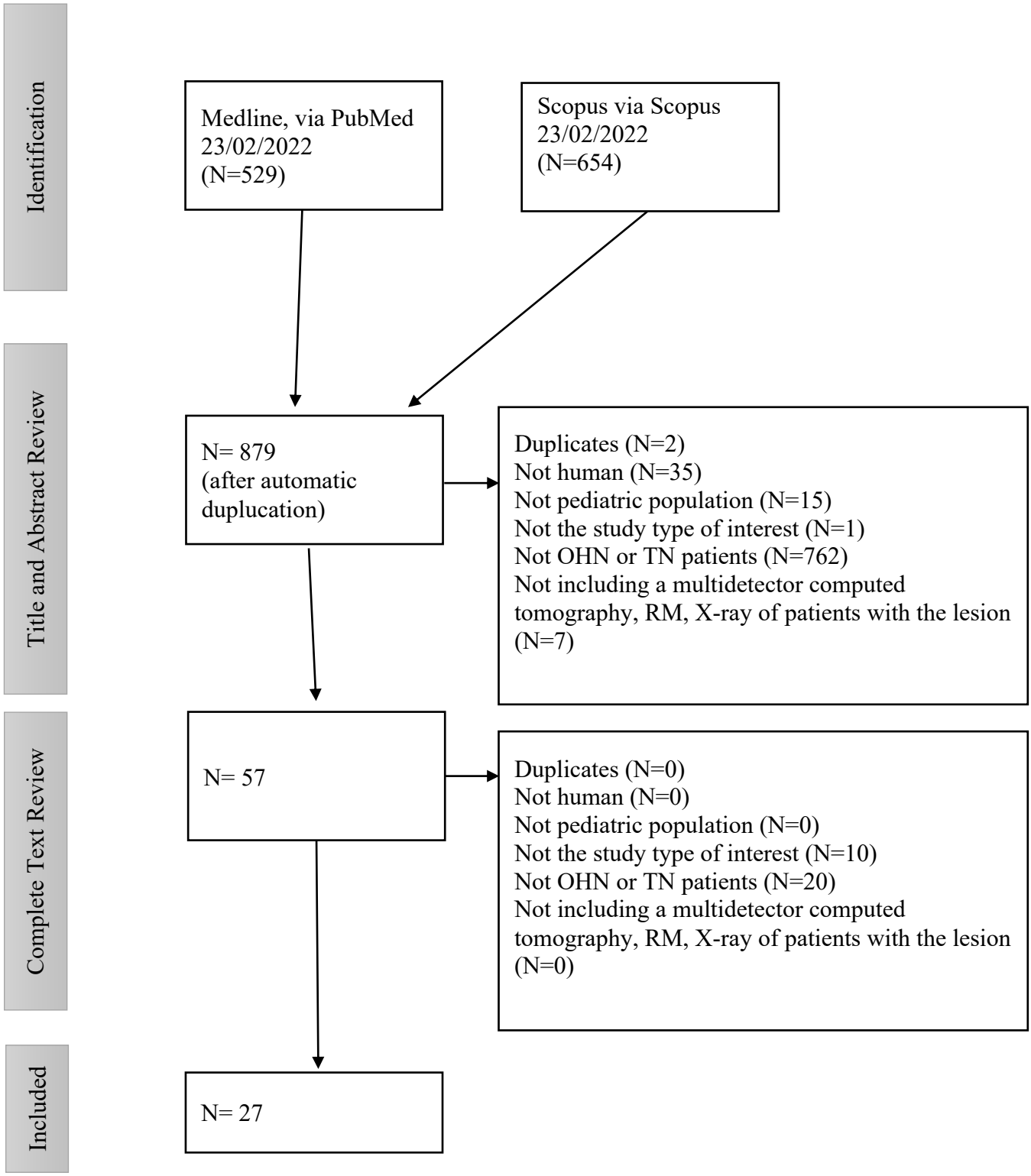

Table 4. Studies included in the systematic review
Caption: This table shows the studies included in the systematic review: author, publication year, studie title, journal.

Author	Year	Study title	Journal	Citation
Arduini et al.	2015	A new classification of peri-articular heterotopic ossification of the hip associated with neurological injury: 3D CT scan assessment and intra-operative findings	Bone and Joint Journal	[12]
Carlier et al.	2005	Ankylosing neurogenic myositis ossificans of the hip	Journal of Bone and Joint Surgery - Series B	[22]
Citak et al.	2011	Treatment of heterotopic ossification after spinal cord injury - Clinical outcome after single-dose radiation therapy	Zeitschrift fur Orthopadie und Unfallchirurgie	[23]
Citak et al.	2016	Heterotopic ossification mimicking infection in patients with traumatic spinal cord injury	Technology and Health Care	[15]
Citak et al.	2012	Risk factors for heterotopic ossification in patients with spinal cord injury: A case-control study of 264 patients	Spine	[16]
De l'Escalopier et al.	2019	Resection of heterotopic ossification around the hip after trauma	EFORT Open Reviews	[35]
Genet et al.	2009	Impact of late surgical intervention on heterotopic ossification of the hip after traumatic neurological injury	Journal of Bone and Joint Surgery - Series B	[25]
Hammad et al.	2021	The Surgical Management of the Rare Neurogenic Myositis Ossificans of the Hip: A Report of 3 Cases	J Orthop Case Rep	[14]
Kim et al.	1992	Computerized quantitative radionuclide assessment of heterotopic ossification in spinal cord injury patients	Parapegia	[17]
Ko et al.	2020	Heterotopic ossification with femoral vein compression mimicking deep vein thrombosis	Journal of Vascular Surgery Cases and Innovative Techniques	[36]
Law Ye et al.	2016	Pre-surgical CT-assessment of neurogenic myositis ossificans of the hip and risk factors of recurrence: A series of 101 consecutive patients	BMC Musculoskeletal Disorders	[37]
Ledermann et al.	2002	Pelvic heterotopic ossification: MR imaging characteristics	Radiology	[38]
Lima et al.	2014	The Use of SPECT/CT in the evaluation of heterotopic ossification in para/tetraplegics	Acta Ortopedica Brasileira	[18]
Liu et al.	2014	Anatomical details of neurogenic heterotopic ossification anterior to the ankylotic hip	Pathology Research and Practice	[39]

Mavrogenis et al.	2012	A classification method for neurogenic heterotopic ossification of the hip	Journal of Orthopaedics and Traumatology	[40]
Mckean et al.	2021	Pelvic MRI in spinal cord injury patients: incidence of muscle signal change and early heterotopic ossification	Spinal Cord	[41]
McMahon et al.	2020	Heterotopic ossification leading to ureteral obstruction resulting in nephrectomy	Journal of Endourology Case Reports	[42]
Ohlmeier et al.	2017	Muscle localization of heterotopic ossification following spinal cord injury	Spine Journal	[19]
Rawat et al.	2019	Incidence and characteristics of heterotopic ossification after spinal cord injury: a single institution study in India	Spinal Cord Series and Cases	[21]
Rosteious et al	2017	The sensitivity of ultrasound screening examination in detecting heterotopic ossification following spinal cord injury	Spinal Cord	[43]
Sautter-Bih et al.	2001	Fractionated and single-dose radiotherapy for heterotopic bone formation in patients with spinal cord injury	Strahlentherapie und Onkologie	[26]
Svircev et al.	2008	False-negative triple-phase bone scans in spinal cord injury to detect clinically suspect heterotopic ossification: a case series	J Spinal Cord Med	[44]
Taly et al.	2001	Neurogenic heterotopic ossification: A diagnostic and therapeutic challenge in neurorehabilitation	Neurology India	[24]
Varghese et al.	1991	Nonarticular complication of heterotopic ossification: A clinical review	Archives of Physical Medicine and Rehabilitation	[13]
Wick et al.	2005	Magnetic resonance signal alterations in the acute onset of heterotopic ossification in patients with spinal cord injury	European Radiology	[45]
Yoon et al.	2018	Ankylosing Neurogenic Myositis Ossificans of the Hip: A Case Series and Review of Literature	Hip Pelvis	[46]
Zellig et al.	2007	Heterotopic ossification of the vocal cords after spinal cord injury	Journal of Spinal Cord Medicine	[20]

The years of publication varied between 1991 [13] and 2021 [14]. 12 studies were undertaken in European countries, mainly in Germany, followed by Middle Eastern countries without differences in terms of HO or radiological methods used in these regions.

Among the 27 articles analyzed, there was a predominant male population (20/27 articles), which is in agreement with the literature [6,7]. In most of the articles mentioned (18/27 studies), tomography was used as the preferred method for the diagnosis of early neurogenic heterotopic ossification which was followed by radiography and magnetic resonance imaging. Tomography, radiography, and MRI were used without finding any major differences for these findings. In two studies [15,16] ultrasound was used initially with radiologists trained in this type of ultrasound; however, findings were confirmed with tomography. Kim et al [17] showed that bone scintigraphy was used after checking HO by radiography. In Lima et al [18], SPECT/CT was used for the diagnosis of this pathology.

The diagnosis of HO developed between the ages of 16 and 75. Most patients presented brain injury with time intervals between 1 to 3 months since the initial injury and the development of HO. Early findings were obtained in 20 articles that included incipient ossifications, ossifications, and categories one to three in the Brooker scale. Late findings such as ankylosis were found only in 2 articles, whereas both types of findings were found in participants of five articles (Table 5).

Table 5 Early and late findings in heterotopic ossification.
Caption: This table shows early and late findings in heterotopic ossification.

Author	**Year**	**Hallazgos tempranos**	**Hallazgos tardíos**
Arduini et al.	2015	Ossification 22/73. movement limitation	51/73 – Ankylosis.

Carlier et al.	2005	Ossification.	NR
Citak et al.	2011	Ossification.	NR
Citak et al.	2016	Yes. Does not specify.	NR
Citak et al.	2012	Yes. Does not specify.	NR
Escalopier et al.	2019	Osificación	NR
Genet et al.	2009	NR	Ankylosis associated with osteopenia.
Hammad et al.	2021	Ossification.	NR
Kim et al.	1992	17 patients, does not specify.	NR
Ko et al.	2020	Ossification around the femoral head, associated with soft tissue edema and femoral venous compression.	NR
Law-Ye et al.	2016	Osteoma.	Ankylosis (33 patients)
Ledermman et al.	2002	Grade 1 (20/141 sites), Grade 2 (39/141), Grade 3 (30/131).	Mature ossification 2n 52/141 affected sites (grade 4).
Lima et al.	2014	Ossification	NR
Liu et al.	2014	Yes in 13/15 patients, does not specify.	Ankylosis (2/15 casos)
Mavrogenis et al.	2012	NR	Ankylosis all patients.
Mckean et al.	2021	Yes. Does not specify.	NR
McMahon et al.	2020	Yes. Does not specify.	NR
Ohlmeier et al.	2017	Yes. Does not specify.	Ankylosis in 4 patients
Rawat et al.	2019	Yes. Does not specify.	NR
Rosteius et al.	2017	Yes. Does not specify.	NR
Sautter et al.	2001	Incipient ossifications (50 joints)	NR
Svircev et al.	2008	Yes. Does not specify.	NR
Taly et al	2001	Yes. Does not specify.	NR
Varghese et al.	1991	Yes. Does not specify.	NR
Wick et al.	2005	Yes. Does not specify.	NR
Yoon et al.	2018	Yes. Does not specify.	NR
Zellig et al.	2007	Yes, ossified arythenoids.	NR

The process of HO evolution varied due to reports of development between 3 and 80 months. [17]. In some studies, HO resection was performed in a time interval between 6 and 285 months (only in the studies that mentioned these findings). The mostly affected anatomic site was the hip joint (approximately 12 studies), as in Arduini et al[12], mainly unilateral. However, studies were observed in which the condition was bilateral [19]. In an unusual way [20], Heterotopic ossification was observed in the vocal cords associated to spinal cord injury. It was also found

that, in some patients, there was involvement in more than one joint [21]. Recurrence of this pathology was observed in a few studies, as in Carlier et al. [22]. In the studies reviewed, only three of them presented deep vein thrombosis as a risk factor and complication for HO [13,23,24]. In Varghese et al [13], it was observed that some participants developed complications such as peripheral nerve palsy and lymphedema.

Table 6 Data extraction table- Objectives.
Caption: This table shows the objectives from all the studies included in the systematic review.

Author	Year	Objective
Arduini et al.	2015	We propose a new 3D-CT classification of neurogenic peri-articular HO of the hip in an attempt to improve surgical planning of the excision operation.
Carlier et al.	2005	NR
Citak et al.	2011	To determine the clinical outcome after single dose radiotherapy in HO prophylaxis in paraplegic patients.
Citak et al.	2016	To review potential "early indicator symptoms" in patients suffering from heterotopic ossification after spinal cord injury, with particular attention to elevated serum CRP, serum CK, and body temperature.
Citak et al.	2012	To analyze the risk factors associated with the development of heterotopic ossification (HO) in patients with traumatic spinal cord injury.
De l'Escalopier et al.	2019	NR
Genet et al.	2009	To investigate the impact of late surgical intervention in patients with hip HO.
Hammad et al.	2021	Evaluate surgery and conservative management of 3 cases with HO
Kim et al.	1992	We evaluated the progression of heterotopic ossification (HO) in 17 patients with spinal cord injury by comparing radiographs, quantitative radionuclide bone scans, and serum alkaline phosphatase levels. provide a quantitative assessment of HO progression in a series of spinal cord patients.
Ko et al.	2020	NR
Law Ye et al.	2016	To describe the preoperative findings of patients with NMO of the hip using biphasic computed tomography (CT). Neurogenic Myositis Ossificans (NMO)
Ledermann et al.	2002	To assess magnetic resonance imaging (MRI) signal intensity characteristics of pelvic heterotopic ossification (HO) at various stages of maturation.
Lima et al.	2014	Evaluate the maturational stage and metabolism of neurogenic heterotopic ossification by using SPECT/CT.
Liu et al.	2014	NR

Mavrogenis et al.	2012	NR
Mckean et al.	2021	To assess changes in pelvic MRI muscle signal and its association to early heterotopic ossification (HO) in patients with spinal cord injuries.
McMahon et al.	2020	NR
Ohlmeier et al.	2017	To analyze the prevalence of early HO in hip muscle groups in 267 patients with spinal cord injuries.
Rawat et al.	2019	To study the incidence and characteristics of heterotopic ossification (HO) after spinal cord injury.
Rosteious et al	2017	To analyze the role of ultrasound in the detection of heterotopic ossification (HO) after spinal cord injury (SCI).
Sautter-Bih et al.	2001	The objective of the present study is to evaluate whether irradiation early in the course of the disease prevents the manifestation of heterotopic ossifications and whether it is effective in preventing re-ossification after surgical treatment.
Svircev et al.	2008	This retrospective study evaluates whether patients with clinically suspicious but negative triphasic nuclear bone scans develop delayed positive nuclear bone scans.
Taly et al.	2001	This report describes patients with NHO, seen at the Neurological Rehabilitation Unit, National Institute of Mental Health and Neurosciences, Bangalore, India.
Varghese et al.	1991	The purpose of this paper is to discuss some cases of non-articular complications of HO that were treated at our hospital.
Wick et al.	2005	The purpose of our study was to evaluate the magnetic resonance imaging (MRI) signal characteristics of acutely forming heterotopic ossification (HO) in paralyzed patients.
Yoon et al.	2018	To assess the clinical and radiological outcomes and review relevant considerations for surgical resection of NMO of the hip joint.
Zellig et al.	2007	To report a rare complication of heterotopic ossification of the vocal cords after spinal cord and multiple organ injuries.

*NR: not reported

Table 7 Data extraction table – Demographic data.
Caption: This table shows the data extraction about number of patients, mean age and gender from the participants of all the studies included in the systematic review.

Author	Year	Number of patients		Mean age (years)	Gender
		Total	Included		
Arduini et al.	2015	55	55	41	Male: 33, female: 22
Carlier et al.	2005	29	29	45,5	Male: 22, female: 7
Citak et al.	2011	75	62	NR	NR
Citak et al.	2016	235	15	30,6	Male: 13, female: 2
Citak et al.	2012	262	132	NR	Male:111 , female: 21
De l'Escalopier et al.	2019	377	293	NR	NR
Genet et al.	2009	143	143	34,5	Male:114 , female:29
Hammad et al.	2021	3	3	16-37	NR
Kim et al.	1992	17	17	28 y 68	Male: 17, female:0
Ko et al.	2020	1	1	33	Male: 1, female:0
Law Ye et al.	2016	101	101	46	Male:83 , female:18
Ledermann et al.	2002	105	36	43.4	Male: 33, female:3
Lima et al.	2014	12	12	39	Male:12 , female:0
Liu et al.	2014	15	15	38,1 ± 14,5	Male:15 , female:0
Mavrogenis et al.	2012	24	24	38	Male: 17, female:7
Mckean et al.	2021	46	40	41	Male: 32, female:8
McMahon et al.	2020	1	1	67	Male: 1, female:0
Ohlmeier et al.	2017	267	267	46	Male: 228, female:39
Rawat et al.	2019	303	303	35	Male:17 , female:2
Rosteious et al	2017	268	217	46,5	Male:185 , female:32
Sautter-Bih et al.	2001	52	52	35	Male:44 , female:8
Svircev et al.	2008	343	343	NR	NR
Taly et al.	2001	377	15	NR	NR
Varghese et al.	1991	43	43	16-59	NR
Wick et al.	2005	45	14	17-79	NR
Yoon et al.	2018	6	6	40	Male: 6, female:0
Zellig et al.	2007	1	1	55	Male:1 , female:0

*NR: not reported,

Table 8 Data extraction table- Study types, investigation period and neurological trauma type.
Caption: This table shows the data extraction about study types, investigation period and neurological trauma type from all the studies included in the systematic review.

Author	Year	STUDY TYPE	Investigation period	Type of neurological trauma:
		1. Prospective. 2.Retrospective. 3. Does not apply 4.Does not specify		1. BRAIN DAMAGE 2. MEDULAR DAMAGE 3. BOTH

				4. OTHERS: VASCULAR DISEASES, LONG STAY IN INTENSIVE CARE UNIT
Arduini et al.	2015	2	1999-2012	3
Carlier et al.	2005	1	1995-2002	4
Citak et al.	2011	4	2006-2009	3
Citak et al.	2016	2	2004-2013	2
Citak et al.	2012	2	2002-2010	2
De l'Escalopier et al.	2019	4	1993-2016	3
Genet et al.	2009	1	1997-2007	3
Hammad et al.	2021	1	2016-2020	3
Kim et al.	1992	3	NR	2
Ko et al.	2020	3	NR	2
Law Ye et al.	2016	2	2006 - 2012	4
Ledermann et al.	2002	2	1995-2000	4
Lima et al.	2014	3	NR	NR
Liu et al.	2014	1	2009-2012	NR
Mavrogenis et al.	2012	2	2002- 2008	3
Mckean et al.	2021	1	2012- 2014	4
McMahon et al.	2020	3	NR	2
Ohlmeier et al.	2017	2	2001- 2014	NR
Rawat et al.	2019	2	2001- 2017.	2
Rosteious et al	2017	2	2003- 2013	NR
Sautter-Bih et al.	2001	2	1989 -2000	NR
Svircev et al.	2008	2	2002 -2004	NR
Taly et al.	2001	1	NR	4
Varghese et al.	1991	4	NR	3
Wick et al.	2005	2	1998- 2003	NR
Yoon et al.	2018	2	2015 -2017	3
Zellig et al.	2007	NR	NR	2

*NR: not reported,

Table 9 Data extraction table- Patients with brain or medullar damage, imaging method, HO anatomical location, complications. Caption: This table shows the data extraction about patients with brain or medullar damage, imaging method, HO anatomical location, complications

Author	**Year**	**Number of patients with brain damage**	**Number of patients with medullar damage**	**Mean time between the initial medullar injury and the development of HO**
Arduini et al.	2015	39	16	NR
Carlier et al.	2005	12	7	NR
Citak et al.	2011	0	0	58.2 days (12-125)
Citak et al.	2016	0	15	49.4 days (16-131)
Citak et al.	2012	0	NR	1 -6 months
De l'Escalopier et al.	2019	189	104	NR
Genet et al.	2009	118	65	4 -12 weeks
Hammad et al.	2021	NR	NR	NR
Kim et al.	1992	0	17	1-3 months
Ko et al.	2020	0	1	NR

Law Ye et al.	2016	48	8	NR
Ledermann et al.	2002	0	31	4 y 12 weeks, 2 - 5 months
Lima et al.	2014	NR	NR	First four weeks after the accident
Liu et al.	2014	NR	NR	NR
Mavrogenis et al.	2012	16	8	NR
Mckean et al.	2021	NR	33	NR
McMahon et al.	2020	0	1	NR
Ohlmeier et al.	2017	NR	NR	63,3 days ± 39,0
Rawat et al.	2019	0	9	3-6 months, 7-12 months
Rosteious et al	2017	NR	NR	62,4 days
Sautter-Bih et al.	2001	NR	NR	3 months
Svircev et al.	2008	NR	NR	NR
Taly et al.	2001	NR	NR	NR
Varghese et al.	1991	23	6	NR
Wick et al.	2005	NR	NR	NR
Yoon et al.	2018	1	5	NR
Zellig et al.	2007	0	1	3 months after withdrawal of mechanical ventilation
Author	**Year**	**Most used imaging diagnostic method**	**HO anatomical location**	**Complications in HO patients**
Arduini et al.	2015	TC y TC 3D	Hip	NR
Carlier et al.	2005	TC y TC 3D	Hip	NR
Citak et al.	2011	TC	NR	DVT (19 patients)
Citak et al.	2016	TC	NR	NR
Citak et al.	2012	TC	Hip/pelvic (91.6%); shoulder (4.9%); knee (2.1%); elbow (1.4%)	NR
De l'Escalopier et al.	2019	TC 3D	Hip (55%)	Medullary cord infection (10.3%)
Genet et al.	2009	TC	NR	NR
Hammad et al.	2021	TC y TC 3D	Hip	NR
Kim et al.	1992	RX	NR	NR
Ko et al.	2020	RX y TC	NR	NR
Law Ye et al.	2016	TC	Hip	NR
Ledermann et al.	2002	RX, TC	NR	NR
Lima et al.	2014	SPECT/TC	NR	NR
Liu et al.	2014	RX	NR	NR
Mavrogenis et al.	2012	TC y radioterapia	NR	NR
Mckean et al.	2021	RM	NR	NR
McMahon et al.	2020	TC	NR	Genitourinary obstruction
Ohlmeier et al.	2017	TC y RM	NR	62 patients (23.2%) had concomitant trochanteric bursitis.
Rawat et al.	2019	NR	NR	Pressure ulcers in 16 (84.2%) patients with spinal cord injuries who developed HO, pressure ulcer and the development of HO (P = 0.01).

Rosteious et al	2017	NR	NR	NR
Sautter-Bih et al.	2001	RX Y TC	49 patients (70 joints, 65 hips, three knees, one shoulder, one elbow) were evaluable.	NR
Svircev et al.	2008	MN	HO occurred in the hip (in 3 patients) and in the femur (in 4 patients).	NR
Taly et al.	2001	RX Y TC	NR	DVP
Varghese et al.	1991	RX Y TC	NR	HO bone mass, ulnar nerve compression. lymphedema.
Wick et al.	2005	RM	NR	NR
Yoon et al.	2018	TC	NR	NR
Zellig et al.	2007	TC	NR	NR

*NR: not reported,

Table 10 Data extraction table- Classifications used and conclusions. Caption: This table shows the data extraction about classifications used and conclusions.

Author	Year	Brooker Clasification HO used	Conclusions
Arduini et al.	2015	NR	3D CT is very useful for surgeons to identify the pathological anatomy of periarticular OH of the hip and planning the best surgery approach for its excision.
Carlier et al.	2005	NR	We confirmed the CT description for the site, shape, and relationship to the joint capsule of neurogenic myositis osificans by surgical exploration of each hip.
Citak et al.	2011	69.4% GRADO I; 27.4% GRADO II; 3.2% GRADO III; 0 GRADO IV	Single-dose radiotherapy with 7 Gy in the treatment of heterotopic ossification is an effective option. Higher electrode voltage improves irradiation efficiency and clinical outcome. Essential to outcome is early detection and treatment of HO with single-dose radiation therapy.
Citak et al.	2016	NR	Elevated levels of serum CRP, serum CK, and elevated body temperature in acute spinal cord injuries can be considered indicators for a diagnosis of concomitant HO.
Citak et al.	2012	NR	Patients with associated spasticity and chest trauma, complete injury, pneumonia, presence of tracheostomy, and urinary tract infection were at increased risk of developing OH. Appropriate management of potential risk factors could help reduce the overall incidence of HO and outcome in patients with traumatic spinal cord injury.
De l'Escalopier et al.	2019	NR	The management of polytraumatized patients, who are frequent victims of OHN, and post-traumatic neurological heterotopic ossification surgery should be performed and organized in a center adapted by a multidisciplinary team. Patients require a very good medical-surgical environment; Although the perioperative risks are significant, the clinical results are good and the risk of recurrence is limited in these conditions.
Genet et al.	2009	37% GRADO IV	Our study did not identify OH within the joint space, and we speculate that it is only ankylosis that induces joint degradation. Estimation of bone mineral density at the femoral neck for patients with HO of the hip after CNS injury is essential to assess intraoperative fracture risk and functional outcome. Waiting for ankylosis to form as a result of HO for patients with CNS injuries maximizes the development of intra-articular pathology and osteoporosis and increases the risk of complications during and after surgery.
Hammad et al.	2021	NR	Neurogenic OM of the hip joint introduces a significant limitation in activities of daily living and, therefore, in quality of life. This condition should be aggressively approached and managed surgically when indicated. The exact operative approach and timing of surgery are best determined by clinical, laboratory, and radiological inputs. CT scans with 3D reconstruction provide valuable data to determine the best surgical approach. Bone scans and SAP levels can provide useful information regarding the maturity of the lesion. For OM of the hip joint, surgical management by arthrolysis or total hip replacement, followed by postoperative physical therapy and oral indomethacin, appears to provide satisfactory results.
Kim et al.	1992	NR	In the majority (10 patients out of 17) radiographic evidence of HO maturation preceded that seen on bone scans, the degree of HO did not correlate with the duration of HO progression. The evolution of HO was

			observed to take place over a period ranging from 3 to 80 months, for reasons that are not clear.
Ko et al.	2020	NR	In summary, in bedridden patients with spinal cord injuries presenting with a swollen leg and possible DVT, HO venous compression of the hip or femur should be considered. US examination and CT venography are excellent traditional imaging modalities for diagnosis. Venography in the catheterization suite could be a useful tool for post-treatment evaluation; an additional intervention could also be performed if necessary.
Law Ye et al.	2016	NR	Biphasic enhanced CT allows preoperative evaluation of NMO with good correlation with surgical observations and helps prevent surgical complications.
Ledermann et al.	2002	Grado 1, 39 con grado 2, 30 con grado 3 y 52 con grado 4.	With progressive HO maturity, the intensity of the T2 signal and contrast enhancement decrease, but the intensity of the equivalent signal to fat and cortical bone increases.
Lima et al.	2014	Spinal cord injury time ranged from 3 to 18 years, where 45.5% had spinal cord injury for less than ten years. Of the 16 pelves studied that showed heterotopic ossification on radiography, only two (12.5%) showed marked osteoblastic activity. Five pelfas (31.25%) showed moderate activity; three (18.75%) mild activity; and six hips (37.5%) showed no osteoblastic activity on SPECT/CT examination.	SPECT/CT helps determine which patients are at higher risk of relapse after surgical resection, proving to be a useful imaging study in preoperative evaluation that can be used to determine the postoperative prognosis of these patients. Level of evidence III, Investigation of a diagnostic test. OH is a clinical condition that is detrimental to the rehabilitation and care of patients with spinal cord injury, making it difficult for them to interact socially. SPECT/CT helps determine which patients should be at higher risk of relapse after resection, proving to be a good test in preoperative evaluation. A study in patients with an indication for resection and a previous SPECT/CT examination can corroborate the results of this study, making this test a valuable resource to determine postoperative prognosis.
Liu et al.	2014	NR	Histologically, mature HO has properties similar to normal bone structure, such as mature lamellar bone, cancellous bone, vessels, and bone marrow, and is fundamentally different from ectopic calcification and myositis ossificans. The main limitation of our study is the lack of OM samples. (2) NHO sits in tissue planes without involving the tissue itself. This is very different from traumatic OH in the hip. Traumatic HO often involves or erodes the local muscles, ligaments, or capsule. NHO in this series does not rupture the femoral neurovascular structures. (3) The mature NHO bone, causing ankylosis of the hip, adheres to and fuses with the cortex of the adjacent bone. Normal bone structure must be exposed as a marker to guide resection in order to avoid iatrogenic fracture.
Mavrogenis et al.	2012	NR	In conclusion, the management of patients with neurogenic HO is challenging. A new classification designed specifically for this disorder is needed. Since the trauma of surgery can aggravate the condition, proper staging, preoperative planning, and combined treatment are beneficial.
Mckean et al.	2021	NR	The incidence of HO in this study of patients with spinal cord injuries is 7% and is close to previously published rates. Magnetic resonance imaging using STIR and T1-weighted sequences is useful for imaging HO, but diffusion-weighted sequences were not useful. Increased muscle signal is common and progressive in the first few months after umbilical cord injury and is associated with AIS A injury and the

			development of immature HO. Magnetic resonance imaging ~40 days after injury can help identify individuals at risk for early HO.
McMahon et al.	2020	NR	In conclusion, this is a rare case of HO infiltrating the GU system through the left ureter. Due to the extensive ossification resulting in obstruction of the ureter and the inability to separate the kidney from the psoas, as well as the need for subsequent neurosurgery, a nephrectomy was ultimately decided as the best treatment option. A simple hand-assisted laparoscopic left nephrectomy was performed, which relieved the obstruction.
Ohlmeier et al.	2017	NR	The most common muscle location for the appearance of HO around the hip was the gluteal muscle group. Considering that there are currently no laboratory parameters available for the detection of HO, highly sensitive ultrasound screening examinations should be performed routinely, paying particular attention to the gluteal muscles. In addition, routine examination of range of motion for extension and external rotation of the hip joint is warranted.
Rawat et al.	2019	NR	The incidence of HO was 6.3% at our institution, and the hip joint is the most common site. Due to the presence of limited treatment options, it is important to diagnose HO early in patients with spinal cord injuries based on clinical features and then confirmed with laboratory and imaging tests.
Rosteious et al	2017	NR	The use of ultrasound to detect HO in patients with cord injuries is reliable and has high sensitivity.
Sautter-Bih et al.	2001	NR	The present results suggest that radiotherapy is an effective local treatment option for spinal cord injured patients with heterotopic ossifications. The results of the present study confirm that radiotherapy for the treatment of heterotopic bone formation in patients with spinal cord injury is an effective tool as primary and postoperative therapy. When used as primary treatment, radiation therapy should be performed as soon as possible after disease onset.
Svircev et al.	2008	NR	For patients in whom HO is clinically suspected to be strong but who have negative triphasic bone scans, additional bone scans should be considered to identify those individuals in whom there is delayed imaging of HO.
Taly et al.	2001	NR	In conclusion, this report highlights the occurrence of NHO in a variety of neurological and neurosurgical disorders in a rehabilitation setting. Vigorous unsupervised exercises can contribute to the formation of NHO. The lack of awareness and the absence of pain due to the primary neurological disorder explain the delay in diagnosis. Once fully formed, there is no effective treatment. Therefore, unexplained swelling or reduction in ROM of the paretic limb joints, rapid ESR, and elevated SAP levels should warrant a search for HO. Treatment includes rest of the affected limb in the acute phase and indomethacin and bisphosphonates until signs of inflammation subside and ESR and SAP levels return to normal. Early detection and prompt intervention are essential for limiting disability.
Varghese et al.	1991	NR	Non-articular complications of HO have been infrequently identified in the literature. Of the 43 cases of HO that we reviewed, seven patients developed complications such as venous thrombosis, peripheral nerve paralysis, and lymphedema. We suggest that the following can be concluded from our review: 1. A non-articular complication of HO can occur and should be considered when treating patients with HO. 2. When massive leg swelling occurs, venous compression by an HO mass should be considered the etiology. 3. When radiographic findings reveal an OH mass anterior and medial to the hip, clinicians should closely monitor the onset of vascular compression in the respective lower extremity. 4. Peripheral nerve entrapment, especially at the elbow, can be a

			complication of HO. This can occur in other joints but has not been previously reported. 5. In the management of venous compression, spontaneous resolution may occur (without surgical management), although surgical intervention should be considered if symptoms persist.
Wick et al.	2005	NR	We conclude that MRI reveals a characteristic pattern of muscle and soft tissue signal alterations in the acute onset of HO that can be differentiated from changes related to trauma, tumors, or infection. Generalized edema, often bilateral and diffuse, and contrast enhancement of multiple muscle groups may be seen during the acute onset of HO. Clearly defined areas of non-enhancement in severely inflamed muscles are seen in all patients and may represent focal muscle necrosis or hemorrhage.
Yoon et al.	2018	NR	Surgical excision of the periarticular NMO of the hip joint can be successful, provided adequate preoperative evaluation is performed. Early surgical intervention produces satisfactory results and can prevent the development of intra-articular pathology. CONCLUSION: Surgical treatment of OH of the hip is effective when performed in patients with appropriate indications. Preoperative CT is essential to assess joint spatial change and preoperative planning. Prolonged delay in surgery can cause pathological intra-articular changes, which can affect functional recovery.
Zellig et al.	2007	NR	Heterotopic ossification of the vocal cords is an unusual and rare complication. In this case, the correlation with the IBS is unlikely, due to the location above the neurological level and the atypical location. However, specialists treating patients with spinal cord injuries who have often suffered severe multitrauma injuries should be aware of this potential complication. Vocal cord HO should be considered in the differential diagnosis when upper airway obstruction develops after weaning from mechanical ventilation.

DISCUSSION AND CONCLUSION

This systematic review compiles predominantly observational studies that reflect the presence of heterotopic ossification in 27 different studies that included 1217 participants from around the world. These studies employed tomography (including 3D CT) as the main diagnostic method for early findings, followed by radiography and magnetic resonance imaging that showed no major differences in methods for the diagnosis of late HO. In some studies [15,16], ultrasonography was initially used by experienced radiologists that complementarily performed tomography to reconfirm the diagnosis. HO diagnosis was principally found especially in patients with brain injury and spinal cord injury. A male predominance was evident in the participants and presented an approximate time interval of 1 [25] to 3 months [26] since the initial injury and the development of HO.

Heterotopic ossification is diagnosed mainly with CT and radiography; CT being the gold standard. [27]. In other studies, like Ampadiotaki et al [28], X-ray is used as an initial study and for control, while tomography is recommended for mature HO or mineralization of early lesions, as in our study. Other studies list both X-ray and CT as gold standard methods [27,29,30]. In addition, as discussed in the articles of our review, 3D tomography is currently one of the leading methods for defining the surgical strategy and planning post-operative management through the assessment of the volume and shape of heterotopic ossification, bases of implantation, discontinuity, assessing the state of the joints, the relationship with the veins and arteries, etc [31]. However, a secondary parameter to be considered when determining a patient's method of diagnosis is radiation, which is known to be much higher in CT than in radiography. MRI is the best study to determine the extent of soft tissue edema [32]. In the acute phase, there is an increase in vascularity and tissue density that can be assessed with this

method [27], but it does not play an important role in the early diagnosis of HO [32]. Ultrasound has been shown to be a sensitive imaging modality for soft tissue injuries and calcifications especially in patients who are limited in their mobility [33]; however, in our study ultrasound was little used. The sensitivity and specificity values were not emphasized in the articles of this review probably because of the known sensitivity and specificity of each imaging method according to the type of lesion to be assessed whether it is a bone or soft tissue lesion.

HO manifests mainly at the level of the hip as in Denormandie et al. [31], which agrees with the data from the studies analyzed in older adults. One of the main factors is associated with neurological trauma, either cerebral or spinal cord trauma. In most of the studies, males are associated as a risk factor for HO [6,7,32] which matches the findings presented in this review. Deep vein thrombosis is also associated with HO [34], which was also found in three reviewed articles.

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