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Systematic Review

Evaluating the Outcomes of Vertebral Biopsies Performed in Osteoporotic Vertebral Fractures: A Systematic Review and Meta-Analysis

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Abstract

Background/Objectives: Osteoporotic vertebral fractures (OVFs) are common in older adults. While surgery is generally reserved for unstable or painful fractures, some OVFs conceal underlying malignancies, including metastatic and hematologic cancers. This study aimed to determine the pooled prevalence of unsuspected malignancy in patients initially diagnosed with OVFs. **Methods:** A systematic search of PubMed and Scopus was conducted from inception to September 2025 in accordance with PRISMA guidelines. Eligible studies included adults with presumed OVFs who underwent vertebral biopsy and histopathological evaluation. Prevalence estimates were pooled using a random-effects model, and study quality was assessed with the Newcastle–Ottawa Scale. **Results:** Thirteen studies involving 3513 patients were included. The pooled prevalence of malignancy was 8.0% (95% CI: 5.4–10.6), comprising metastatic solid tumors (4.9%; 95% CI: 2.3–7.4) and multiple myeloma (2.6%; 95% CI: 1.3–3.9). Malignancy was detected in 2.7% (95% CI: 1.8–4.1) of routine biopsy cohorts versus 36.8% (95% CI: 22.1–54.4) of clinically suspected cases. Diagnostic yield exceeded 45% in patients selected by combined history, imaging, or known malignancy. No biopsy-related complications or procedure-related mortality were reported. Moderate heterogeneity was observed, mainly in suspected cohorts. **Conclusions:** Vertebral biopsy is a safe and diagnostically valuable procedure in vertebral compression fractures. Its yield ranges from about one in 30 patients in routine settings to nearly one in two in high-risk groups, underscoring the importance of structured patient selection to facilitate timely cancer detection and referral.

Keywords: osteoporotic vertebral fractures; unsuspected malignancy; vertebral biopsy; metastatic spinal tumors; multiple myeloma

Academic Editor: Umile Giuseppe Longo

Received: 17 August 2025
Revised: 19 September 2025
Accepted: 3 October 2025
Published: 11 October 2025

Citation: Bulut, H.; Lam, C.; Sheth, V.; Ali, I.; Tsagkaris, C.; Jones, M.; Botchu, R.; Errani, C.; Hamzaoglu, A.; Ozkan, K. Evaluating the Outcomes of Vertebral Biopsies Performed in Osteoporotic Vertebral Fractures: A Systematic Review and Meta-Analysis. *Osteology* **2025**, *5*, 30. https://doi.org/10.3390/osteology5040030

1. Introduction

Vertebral fractures represent one of the most common fragility fractures in older adults and are frequently encountered in clinical practice. They typically occur following low-energy trauma, such as a simple fall from standing height, and are widely regarded as a natural consequence of age-related bone loss and osteoporosis. With advancing age, reduced bone mineral density, microarchitectural deterioration, and cumulative risk factors such as postmenopausal estrogen deficiency or chronic glucocorticoid use increase susceptibility to such injuries. In the majority of cases, management is conservative and directed toward pain control, bracing, physical rehabilitation, and pharmacologic treatment for underlying osteoporosis. Surgical interventions are usually reserved for specific scenarios, including cases where patients experience mechanical instability, progressive vertebral deformity, significant neurological compromise, or refractory pain unresponsive to medical therapy [1]. Epidemiologic data suggest that the lifetime risk of sustaining an osteoporotic vertebral fracture ranges from 15% to 25%, underscoring its clinical relevance as a major public health problem and a contributor to disability, morbidity, and healthcare expenditure worldwide [1].

Despite their frequent classification as benign osteoporotic events, a subset of vertebral fractures initially presumed to be osteoporotic are later recognized as secondary to an underlying malignant process. These can include metastatic deposits from solid tumors—most commonly originating from the lung, breast, or prostate—or primary hematologic malignancies such as multiple myeloma or lymphoma [2]. The clinical challenge lies in the fact that these conditions often present without obvious systemic symptoms or a prior history of cancer, thereby mimicking the radiological and clinical features of benign osteoporotic fractures. The overlap in imaging characteristics, particularly in magnetic resonance imaging (MRI) or computed tomography (CT), between acute osteoporotic fractures with bone marrow edema and early malignant infiltration, which further complicates diagnostic accuracy. As a result, the diagnosis of malignancy is frequently delayed, which can adversely influence patient prognosis by allowing disease progression, neurological deterioration, or missed opportunities for timely oncologic therapy [2,3].

Over the past decade, increasing attention has been directed toward the possibility of occult malignancy in patients initially diagnosed with osteoporotic vertebral fractures. Several clinical series and cohort studies have reported non-negligible rates of unsuspected cancer in this setting. However, the reported prevalence varies widely across the literature, ranging from as low as 2% to as high as nearly 15% in some cohorts. This variability is likely attributable to several factors, including differences in the proportion of patients undergoing vertebral biopsy, heterogeneity in imaging protocols, length of follow-up surveillance, and variations in patient selection criteria [2,4–15]. For example, centers that routinely incorporate percutaneous biopsy into vertebral augmentation procedures report lower detection rates, whereas institutions adopting a selective, suspicion-driven approach identify malignancies primarily in clinically atypical cases. Such discrepancies highlight ongoing uncertainties in the diagnostic process and underscore the lack of universally accepted guidelines regarding when biopsy should be performed.

These challenges are further compounded by the complex clinical profiles of elderly patients, who often present with multiple comorbidities and diverse treatment preferences. Decisions regarding whether to pursue invasive diagnostic procedures such as biopsy must therefore balance the potential yield of detecting a malignancy against procedural risks, patient frailty, and anticipated treatment pathways. Nonetheless, missed or delayed recognition of vertebral malignancy has substantial clinical consequences. Early identification of malignant spinal involvement not only facilitates prompt referral to oncology and the

initiation of systemic or local therapies but also provides opportunities to stabilize the spine, prevent neurological compromise, and improve quality of life.

Against this background, the present systematic review and meta-analysis was designed to clarify the true prevalence of occult malignancy in patients who initially present with vertebral fractures presumed to be osteoporotic in origin. By synthesizing evidence across multiple cohorts, the study aims to provide a more precise estimate of this prevalence, thereby guiding clinical decision-making and informing which patients may benefit from advanced diagnostic strategies, particularly vertebral biopsy.

2. Materials and Methods

This study was designed as a systematic review and meta-analysis to determine the frequency of unsuspected malignancies identified through vertebral biopsies in patients initially diagnosed with osteoporotic vertebral fractures (OVFs). To ensure transparency and methodological integrity, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines throughout the process [16] (See Supplementary Materials). The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under ID CRD420251052182 [17].

2.1. Eligibility Criteria

The study included adults (aged 18 years and older) diagnosed with OVFs who subsequently underwent vertebral biopsy or diagnostic evaluation capable of confirming or ruling out malignancy. Eligible studies had to provide either histopathological confirmation of malignancy or radiologic follow-up sufficient to exclude it. Only articles published in peer-reviewed journals and written in English were considered.

The focus was on observational designs—specifically retrospective cohort studies—as they reflect real-world diagnostic practices. We excluded case reports, narrative reviews, conference abstracts, and editorials. Also excluded were studies without confirmed diagnostic outcomes (i.e., those lacking biopsy or adequate follow-up imaging) and those limited to traumatic, infectious, or pediatric vertebral fractures. For this review, "unsuspected malignancy" referred to cancers such as solid tumor metastases, multiple myeloma, or lymphoma discovered during diagnostic workup in patients initially presumed to have benign osteoporotic fractures, without prior clinical suspicion.

2.2. Literature Strategy and Data Sources

Two investigators carried out a comprehensive search of PubMed/MEDLINE and Scopus, covering publications from database inception through September 2025. To minimize publication bias, we also searched OpenGrey for relevant gray literature and manually reviewed the reference lists of all full-text articles that met inclusion criteria. Our search strategy combined both MeSH terms and free-text keywords, including: ("osteoporotic vertebral fracture" OR "compression fracture" OR "vertebral insufficiency fracture") AND ("malignancy" OR "cancer" OR "metastasis" OR "myeloma" OR "neoplasm").

2.3. Study Selection

All references were initially imported into EndNote (EndNote 21) for duplicate removal. The unique records were then uploaded into Covidence, a web-based platform designed to streamline systematic reviews. Two reviewers independently screened all titles and abstracts, followed by full-text review of potentially eligible articles. Any disagreements were resolved through discussion, and when necessary, a third reviewer provided input. We documented the selection process using the PRISMA 2020 flow diagram.

2.4. Data Extraction

A standardized data extraction form was created and pilot-tested on a subset of studies to ensure clarity and consistency. Two reviewers then independently extracted data from the included studies. Extracted variables included:

(1) Study characteristics (authors, publication year, country, and design);
(2) Patient demographics (sample size, age, and sex);
(3) Biopsy technique and imaging modalities used;
(4) Fracture location and how diagnosis was confirmed (biopsy vs. radiologic follow-up);
(5) Outcomes of interest, primarily the prevalence and types of malignancy identified (e.g., solid tumors, multiple myeloma, lymphoma).

Any differences between reviewers were discussed and resolved by consensus.

2.5. Risk of Bias Assessment

To assess study quality, we used the Newcastle-Ottawa Scale (NOS) [18], a validated tool for evaluating observational cohort studies. The scale assesses three domains: selection of participants, comparability of groups, and outcome assessment. Two reviewers independently scored each study, with discrepancies resolved through discussion. Studies receiving a total score between 7 and 9 were considered to have a low risk of bias, while those scoring below 7 were considered to have a higher risk.

2.6. Statistical Analysis

We calculated pooled prevalence estimates for unsuspected malignancies—specifically solid tumor metastases, multiple myeloma, and overall malignancy—using a random-effects model (DerSimonian-Laird method), which accounts for both within- and between-study variability. Heterogeneity was assessed using the I^2 statistic, all reported with 95% confidence intervals. All statistical analyses were performed using the Jamovi software (2.6.44) platform [19].

3. Results

The comprehensive literature search across PubMed/MEDLINE, Scopus, and sources initially yielded 2841 records. After removal of duplicates and rigorous title/abstract screening, 89 articles were assessed at the full-text stage. Of these, 13 studies comprising a total of 3513 patients met all inclusion criteria and were retained for quantitative synthesis. Pooled effect sizes were derived using a random-effects model to accommodate inter-study variation, while heterogeneity was quantified using the I^2 statistic (Figure 1).

3.1. Study Characteristics

The 13 included cohort studies were published between 2008 and 2024, reflecting more than a decade of evolving clinical practice and biopsy protocols in vertebral fracture management (Table 1). Sample sizes ranged widely, from as few as 50 participants in smaller institutional series to more than 1300 in large-scale retrospective cohorts. The average or median age of participants was consistently within the older adult range, spanning 60 to 76 years, which is consistent with the demographic most affected by osteoporotic vertebral compression fractures.

Reported prevalence of malignancy varied considerably between studies, ranging from as low as 2.0% to as high as 46.8%. This striking variability largely reflected differences in patient selection, with some cohorts applying routine biopsy in all patients presenting with presumed osteoporotic fractures, while others restricted biopsy to cases with clinical or radiographic suspicion of underlying malignancy. Malignant diagnoses encompassed a spectrum of conditions: multiple myeloma was reported in eight studies, solid tumor

metastases in nine, and rare primary bone tumors in isolated cases. One study uniquely reported a chondrosarcoma presenting as vertebral collapse, underscoring that primary neoplasms, although rare, must remain within the diagnostic differential.

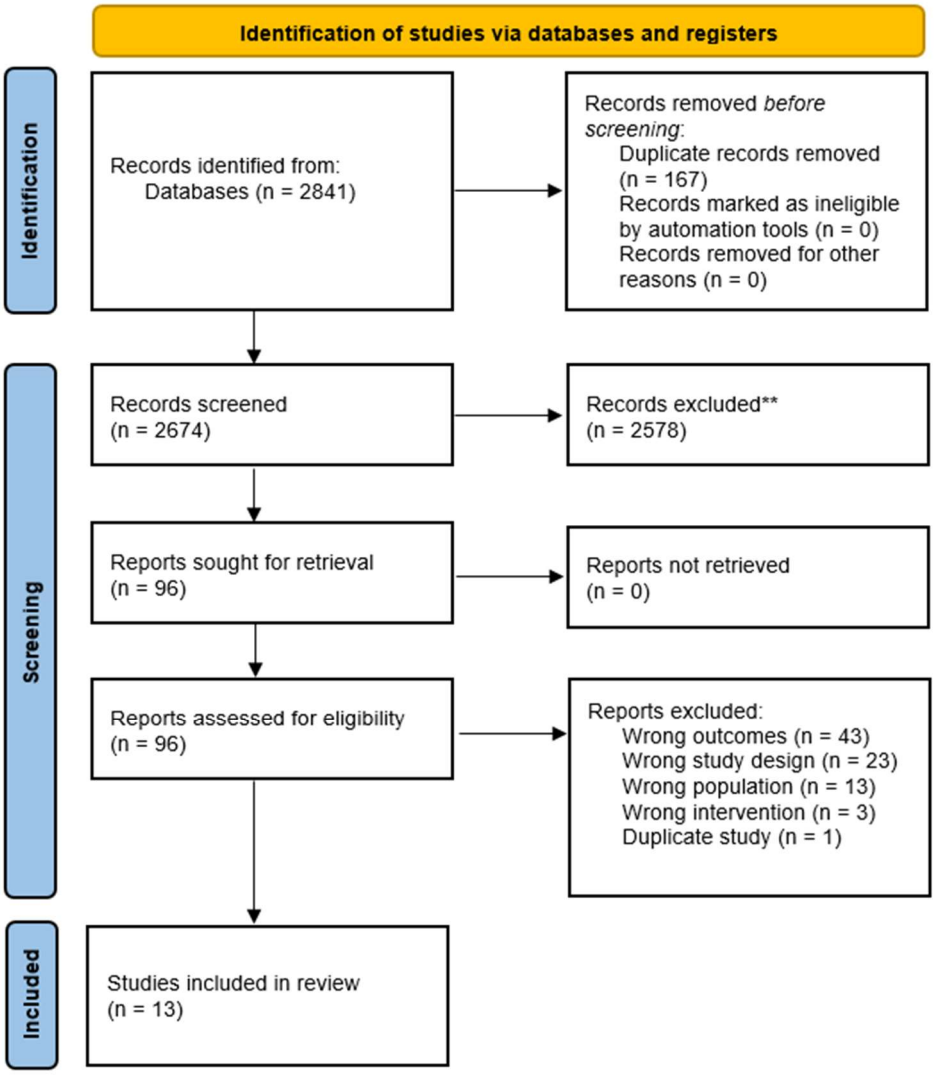

Figure 1. PRISMA Flowchart. ** Note: Double asterisks (**) indicate studies excluded based on our exclusion criteria during the abstract screening stage.

Table 1. Summary of included studies' characteristics.

Author	Year	Patient Count	Malignant Cases	Malignancy (%)	Age (Mean/Median)	Multiple Myeloma (*n*)	Primary Bone Tumors (*n*)	Metastatic Tumors (*n*)
Wickstrøm et al. [4]	2024	459	27	5.88	75	NSM	NSM	NSM
Schoenfeld et al. [5]	2008	50	4	8.00	76	1	0	3
Hershkovich et al. [6]	2020	113	13	11.50	71	9	0	4
Chou et al. [8]	2013	450	61	13.56	—	9	0	52

Table 1. *Cont.*

Author	Year	Patient Count	Malignant Cases	Malignancy (%)	Age (Mean/Median)	Multiple Myeloma (*n*)	Primary Bone Tumors (*n*)	Metastatic Tumors (*n*)
Joseph et al. [12]	2012	56	8	14.29	60	NSM	NSM	NSM
Nowak et al. [15]	2018	97	10	10.31	68	—	0	10
Pagdal et al. [7]	2016	84	10	11.90	63	8	0	2
Venturi et al. [10]	2011	98	2	2.04	73	0	1 (Chondrosarcoma)	1
Jia et al. [13]	2024	1352	44	3.25	70	24	0	20
Muijs et al. [11]	2009	71	3	4.23	73	1	0	0
Jia et al. [20]	2023	156	73	46.79	66	20	0	53
Sozzi et al. [14]	2021	324	20	6.17	73	12	0	8
Pneumaticos et al. [9]	2010	75	11	14.67	69	3	0	8

NSM: not specifically mentioned.

3.2. Prevalence of Solid Tumor Metastases

Across nine studies reporting on solid malignancy, the pooled prevalence of vertebral metastases was 4.87% (95% CI: 2.30–7.44; $p < 0.001$) (Table 2). The most common primary sites mirrored global cancer epidemiology, with breast, lung, colon, prostate, and pancreas predominating. Geographic variation was noted, with breast and lung cancers more frequently encountered in European cohorts, while gastrointestinal primaries such as colon and pancreas appeared more prominently in Asian series.

Table 2. Prevalence of malignancy in vertebral biopsies among patients with osteoporotic fractures.

Diagnosis Category	Pooled Prevalence (%)	95% CI (Lower–Upper)	*p*-Value	Number of Studies (*k*)
Solid Malignancy Metastasis	4.87	2.30–7.44	<0.001	9
Multiple Myeloma	2.62	1.31–3.94	<0.001	8
All Malignant Diagnoses	8.00	5.43–10.60	<0.001	12

3.3. Prevalence of Multiple Myeloma

Eight studies specifically reported on multiple myeloma as a cause of vertebral collapse. The pooled prevalence was 2.62% (95% CI: 1.31–3.94; $p < 0.001$) (Table 2). Although numerically lower than metastases, multiple myeloma comprised a major share of malignant findings in several cohorts, particularly in smaller institutional series where cases of metastatic carcinoma were less common.

3.4. Unsuspected Versus Suspected Biopsy Protocols

Marked differences emerged when comparing routine biopsy strategies with selective biopsy in patients with suspected malignancy (Table 3). In the nine studies that

implemented routine biopsy across 2700 patients, the pooled prevalence of unsuspected malignancy was 2.74% (95% CI: 1.83–4.09), with moderate heterogeneity (I^2 = 41.7%). The prediction interval (1.21–6.12%) confirmed that although most cohorts reported a prevalence within the low single digits, rare studies reported higher rates.

Table 3. Comparison of Unsuspected versus Suspected Biopsy Protocols.

Protocol	*k*	*n*	Malignant Cases	Pooled % (95% CI)	I^2	Prediction Interval
Unsuspected cases	9	2700	72	2.74% (1.83–4.09)	41.7%	1.21–6.12%
Suspected cases	4	271	108	36.77% (22.06–54.44)	82.5%	11.72–71.80%

By contrast, in four studies encompassing 271 patients selected for biopsy on the basis of clinical or radiological suspicion, the prevalence of malignancy was substantially higher at 36.77% (95% CI: 22.06–54.44). Heterogeneity was high (I^2 = 82.5%), and the prediction interval was wide (11.72–71.80%), reflecting variability in suspicion criteria across studies. These findings reinforce that while selective biopsy strategies enrich the yield of malignancy detection, they inevitably miss a measurable proportion of occult cases captured by routine protocols.

3.5. Subgroup Analysis of Suspected Cases

Further subgroup analyses clarified the determinants of suspicion (Table 4). Two studies (*n* = 59) that applied combined clinical history and imaging as selection criteria yielded the highest malignancy rate, 45.8% (95% CI: 33.6–58.6), with no heterogeneity (I^2 = 0%). This underscores the predictive value of integrating patient context, such as weight loss, anemia, or prior malignancy, with radiological features. In contrast, suspicion based on imaging alone yielded a lower rate of 14.3% ([12]; *n* = 56), highlighting the overlap in radiographic characteristics between benign osteoporotic collapse and malignant infiltration. The highest detection rate, 46.8% (95% CI: 39.1–54.6), was reported in a cohort of 156 patients with known malignancy undergoing biopsy to confirm vertebral involvement ([20]).

Table 4. Meta-analysis of Suspected Biopsy Subgroups.

Subgroup	*k*	*n*	Malignant Cases	Pooled % (95% CI)	I^2	Prediction Interval
History + Imaging	2	59	27	45.8% (33.6–58.6)	0%	33.6–58.6%
Imaging-only suspicion	1	56	8	14.3% (7.3–26.1)	–	7.3–26.1%
Known malignancy history	1	156	73	46.8% (39.1–54.6)	–	39.1–54.6%

3.6. Complications

Across all 13 studies and 3513 patients, no biopsy-related complications, mortality, or adverse events were reported.

3.7. Bias Assessment

Risk of bias was systematically assessed using the Newcastle–Ottawa Scale (NOS) (Table 5). Overall, methodological quality was high. Eleven studies achieved a maximum score of 9/9, indicating robust design with strong representativeness, appropriate comparator groups, reliable ascertainment of exposure, and adequate follow-up. Two studies scored 7 due to limitations in cohort representativeness, largely reflecting single-center design with narrow demographic catchment. Importantly, there was no indication of systematic outcome reporting bias, and the consistency of results across settings strengthens the external validity of the findings.

Table 5. Newcastle-Ottawa Scale (NOS) Bias Assessment for Included Cohort Studies. Each ★ on the Newcastle–Ottawa Scale (NOS) is worth 1 point.

Study	Representativeness of Exposed Cohort	Selection of Non-Exposed	Ascertainment of Exposure	Outcome Not Present at Start	Comparability	Assessment of Outcome	Adequate Follow-Up Length	Adequacy of Follow-Up	Total Score (Max 9)
Wickstrøm et al. (2024) [4]	★	★	★	★	★★	★	★	★	9
Schoenfeld et al. (2008) [5]	★	★	★	★	★★	★	★	★	9
Hershkovich et al. (2020) [6]	★	★	★	★	★★	★	★	★	9
Chou et al. (2013) [8]		★	★	★	★★	★	★	★	8
Joseph et al. (2012) [12]		★	★	★	★★	★	★	★	8
Nowak et al. (2018) [15]		★	★	★	★★	★	★	★	8
Venturi et al. (2011) [10]	★	★	★	★	★★	★	★	★	9
Jia et al. (2024) [13]			★	★	★★	★	★	★	7
Jia et al. (2023) [20]			★	★	★★	★	★	★	7
Muijs et al. (2009) [11]	★	★	★	★	★★	★	★	★	9
Sozzi et al. (2021) [14]		★	★	★	★★	★	★	★	8
Pneumaticos et al. (2010) [9]	★	★	★	★	★★	★	★	★	9
Pagdal et al. (2016) [7]	★	★	★	★	★★	★	★	★	9

4. Discussion

4.1. Principal Findings

This meta-analysis provides compelling evidence in favor of incorporating vertebral body biopsy into the diagnostic pathway for OVFs. Across 13 cohort studies and more than 3500 patients, biopsies consistently revealed a clinically relevant prevalence of malignancy, with an overall pooled rate of 8%. Importantly, in routine biopsy protocols—where patients had no clinical or radiological suspicion—malignancies were still identified in nearly 3% of cases. This yield equates to approximately one in thirty patients, a figure that challenges the assumption that vertebral fractures in elderly individuals are uniformly benign. Although 3% may initially appear numerically modest, it represents a clinically significant burden when extrapolated to the population level. OVFs account for more than 1.4 million new cases annually worldwide, with lifetime risks in women approaching 25% [1]. Applying the 3% malignancy rate to these figures suggests that tens of thousands of patients each year could harbor previously unsuspected cancer [2,4–15]. In high-risk subgroups, such as those with prior malignancy or atypical imaging features, the probability rises dramatically, as our pooled estimate of 37–45% demonstrates. Thus, vertebral biopsy is not simply a niche intervention but has the potential to alter the diagnostic trajectory of a substantial number of patients globally. Safety data were consistent across all included studies, with no biopsy-related complications, morbidity, or mortality reported. This finding is especially noteworthy because even low-frequency adverse events can become meaningful when procedures are applied widely in elderly populations. The absence of complications across >3500 cases reinforces that biopsy is not only diagnostically valuable but also practical and safe for integration into routine care. Together, these findings indicate that vertebral

biopsy can function both as an opportunistic screening strategy in routine cases and as a high-yield diagnostic safeguard in clinically suspicious presentations.

4.2. Comparison with Existing Literature

Our pooled prevalence estimates align with but also extend prior single-center reports. Earlier retrospective cohorts from tertiary spine oncology centers reported malignancy detection rates ranging from 5% to 15% in patients initially labeled as osteoporotic fracture cases [2,4–15,20–23]. However, those series often lacked systematic biopsy protocols and were prone to referral bias, as tertiary centers are more likely to receive diagnostically complex cases. By synthesizing data across more than a decade and multiple geographic regions, our study provides a more robust prevalence estimate. Across studies, no specific demographic comparisons or subgroup risk analyses were reported. Variation in the observed prevalence instead appears to stem primarily from differences in biopsy strategy. Cohorts that incorporated routine vertebral biopsy during augmentation tended to detect a greater absolute number of occult malignancies, whereas series restricting biopsy to radiologically or clinically suspicious cases yielded higher positivity rates among biopsied patients but offered less generalizability to unselected populations. This methodological heterogeneity—further compounded by disparate imaging protocols and follow-up durations—likely accounts for much of the between-study variability and underscores the absence of universally adopted indications for vertebral biopsy. In comparison with prior systematic reviews in osteoporosis and spinal oncology, our findings confirm that vertebral biopsy is underutilized despite its diagnostic yield. Most published reviews have emphasized the radiological hallmarks of malignant versus benign fractures—such as pedicle involvement, posterior wall bulging, or diffuse marrow signal—but few have provided pooled quantitative estimates of biopsy-proven malignancies. By integrating these data, our meta-analysis establishes a firmer evidence base for considering biopsy in broader clinical practice. Furthermore, our work adds to the literature by demonstrating not only the prevalence of malignancy but also the consistently favorable safety profile of biopsy, strengthening the case for its wider application. Moreover, variation in diagnostic yield across the literature reflects not only geographic and practice-pattern differences but also methodological diversity. Some cohorts mandated histopathological review by subspecialty musculoskeletal pathologists, while others relied on general pathology services, potentially affecting sensitivity for subtle hematologic malignancies such as myeloma. Our findings therefore suggest that establishing uniform diagnostic pathways could reduce heterogeneity and provide a more reliable benchmark for clinical practice.

4.3. Biopsy Versus Imaging in Diagnostic Accuracy

Imaging modalities such as MRI, CT, and PET are invaluable in the initial evaluation of vertebral fractures, yet they carry inherent limitations in differentiating benign osteoporotic collapse from malignant infiltration [2,4–15,23–27]. MRI remains the most sensitive modality for detecting marrow replacement, with reported sensitivities exceeding 90% in some series. However, overlap in signal characteristics—particularly between acute osteoporotic fractures with edema and early metastatic lesions—can yield false negatives or equivocal results. CT improves visualization of cortical destruction and pedicle involvement, but its sensitivity for early marrow disease is limited. PET-CT provides metabolic information and can detect systemic disease, but uptake can be nonspecific in acute benign fractures or inflammatory conditions, leading to false positives. In contrast, biopsy offers histopathologic confirmation with near-absolute specificity. Several studies included in our analysis highlighted cases where imaging suggested benign osteoporotic collapse, yet biopsy revealed multiple myeloma or metastatic carcinoma. Conversely, biopsy avoided overtreatment in

instances where imaging raised unwarranted suspicion, confirming a purely osteoporotic etiology. These observations underscore that while imaging is indispensable for triage and surveillance, it cannot reliably exclude malignancy in ambiguous cases.

4.4. Patient Selection and Triage for Biopsy

Although imaging is central to the evaluation of vertebral compression fractures, its limitations necessitate a structured approach to patient selection for biopsy. The evidence synthesized in this review suggests that clinical, laboratory, and radiological features can be stratified into high, moderate, and low–moderate suspicion levels.

High suspicion cases include patients with a prior history of malignancy combined with characteristic imaging findings such as pedicle or posterior element destruction, convex posterior vertebral wall, paraspinal or epidural soft-tissue masses, or diffuse marrow signal abnormalities on MRI [8,11,20]. In such circumstances, biopsy should be considered mandatory.

Moderate suspicion arises in the presence of atypical age, absence of conventional osteoporosis risk factors, unexplained laboratory abnormalities (e.g., anemia, elevated ESR, hypercalcemia, M-protein spike), or clinical features such as nocturnal/progressive pain or neurological decline [7,12,15]. Biopsy is strongly recommended in these cases, even when imaging is equivocal.

Low–moderate suspicion corresponds to radiologically typical osteoporotic fractures in patients without systemic risk factors. Although the absolute probability of malignancy is low, large series still report detection rates of 2–3%. In these scenarios, opportunistic biopsy performed during planned kyphoplasty or vertebroplasty represents a pragmatic, low-morbidity approach [9,14,22].

Taken together, these findings support a tiered triage framework in which biopsy is used not only as a safeguard in clinically suspicious presentations but also as an opportunistic diagnostic tool in routine cases. This structured approach may facilitate guideline development, reduce heterogeneity in clinical practice, and improve early cancer detection in patients initially presumed to have benign osteoporotic fractures (Table 6).

Table 6. Suspicion Criteria for Malignancy in Vertebral Compression Fractures.

Domain	Suspicion Criterion	Clinical/Diagnostic Rationale	Suspicion Level	Recommendation	Key References
Clinical	Prior history of malignancy	Patients with known cancer have the highest rate of malignant VCFs (≈45–47%).	High	Always biopsy	[11,13,20]
	Age/osteoporosis mismatch	Younger patients or those without osteoporosis risk factors should raise suspicion.	Moderate	Biopsy strongly recommended	[12,15]
	Persistent, nocturnal, or progressive pain	Uncharacteristic for benign OVFs; often indicates pathological fracture.	Moderate–High	Biopsy	[12]

Table 6. *Cont.*

Domain	Suspicion Criterion	Clinical/Diagnostic Rationale	Suspicion Level	Recommendation	Key References
	Neurological deterioration	Suggests epidural/paraspinal involvement by tumor.	High	Biopsy + urgent oncologic workup	[10]
Laboratory	Anemia, high ESR/CRP, hypercalcemia, M-protein spike	Classic for multiple myeloma or systemic malignancy.	Moderate–High	Biopsy to confirm	[7]
Imaging (CT/MRI)	Pedicle or posterior element destruction	Rare in benign OVF; strong predictor of malignancy.	High	Biopsy	[8]
	Convex posterior vertebral wall	Non-osteoporotic feature; indicates infiltration.	High	Biopsy	[8]
	Paraspinal or epidural soft-tissue mass	Direct evidence of tumor extension.	High	Biopsy	[8]
	Diffuse marrow signal abnormality on MRI	Suggests infiltrative process (myeloma/metastasis).	High	Biopsy	[8]
	Multiple non-adjacent lesions	More consistent with metastatic disease than osteoporosis.	High	Biopsy	[11]
Diagnostic performance	"Benign-appearing" MRI but cancer history	11/427 MRI-benign cases revealed malignancy only on biopsy; sensitivity rose from 59% → 85% when clinical history was added.	Moderate–High	Biopsy despite negative imaging	[4,5]
Triage guidance	High suspicion = history of cancer + ≥1 imaging red flag.	High probability of malignant VCF.	High	Definite biopsy	[8]
	Moderate suspicion = equivocal MRI, clinical/lab mismatch.	Diagnostic uncertainty.	Moderate	Strongly recommend biopsy	[12]
	Low–moderate suspicion = typical osteoporotic VCF, no risk factors.	Still 2–3% malignancy detection even in "benign" cases.	Low–Moderate	Opportunistic biopsy during kyphoplasty/ vertebroplasty	[2,6,9,14,28]

4.5. Clinical Benefits of Early Diagnosis for Patient Management

The detection of unsuspected malignancies in patients presumed to have benign fractures carries profound clinical consequences [28–36]. First, early identification of metastatic disease enables timely initiation of systemic and surgical therapy. In several included studies, early intervention has several advantages in the management of metastatic spine cases [33–36]. Without biopsy confirmation, such individuals might have continued to receive only analgesia or osteoporosis-directed therapy, thereby missing the therapeutic window for oncologic intervention. Second, biopsy provides essential guidance for radi-

ation therapy planning. Vertebral metastases are often managed with stereotactic body radiotherapy (SBRT) or conventional fractionated schedules. A biopsy that confirms malignancy enables accurate field definition, ensures correct dosing, and prevents unnecessary irradiation in benign cases. Conversely, a negative biopsy spares patients the morbidity of inappropriate radiation and its attendant risks, including vertebral collapse and radiation-induced myelopathy.

Third, surgical decision-making is directly influenced by biopsy findings. In a purely osteoporotic fracture, percutaneous cement augmentation may be sufficient to stabilize pain and prevent further collapse. However, if biopsy confirms metastatic involvement, more robust interventions—such as instrumented fixation or en bloc resection—may be required to prevent neurological deterioration. Similarly, biopsy confirmation of multiple myeloma often shifts management toward systemic therapy and radiotherapy rather than aggressive surgical stabilization. These distinctions illustrate that biopsy does not merely provide diagnostic clarity but also directly shapes the therapeutic trajectory.

Beyond oncologic planning, early biopsy-based diagnosis has broader implications for patient quality of life [37,38]. Preventing progressive vertebral collapse and neurological compromise reduces hospitalizations, preserves ambulation, and maintains independence in elderly populations. Importantly, the diagnosis of an unsuspected malignancy also initiates timely palliative care discussions when curative treatment is not feasible, allowing patients and families to make informed choices about goals of care.

Equally important are the implications for palliative versus curative decision-making. In many elderly patients, a new cancer diagnosis reframes therapeutic goals toward symptom control and preservation of independence, rather than aggressive survival-prolonging interventions. Biopsy provides clarity that allows clinicians to align treatment intensity with patient values. In contrast, for younger or fitter patients with oligometastatic disease, early biopsy confirmation can open the possibility of curative local therapy combined with systemic management. Patient-reported outcomes also deserve emphasis: several observational studies have shown that timely diagnosis of vertebral malignancy improves pain control, reduces opioid dependence, and enhances functional recovery compared with delayed recognition. These findings reinforce that the value of biopsy extends beyond oncologic accuracy into meaningful quality-of-life gains.

4.6. Health Economics and Policy Considerations

From a health systems perspective, vertebral biopsy represents a low-cost intervention with potential for substantial downstream savings. The incremental costs of adding biopsy to a planned kyphoplasty or vertebroplasty are minimal—requiring only additional needles and pathology processing—while the financial burden of a missed malignancy can be considerable [6]. Delayed cancer diagnoses often culminate in emergency admissions for cord compression, prolonged inpatient stays, and costly salvage interventions such as decompression and stabilization surgery [32–35,37,38]. In addition, missed opportunities for earlier systemic therapy can reduce survival, leading to both human and economic costs [28,33,34].

Cost-effectiveness analyses in related fields provide a useful analogy. The 3% malignancy detection rate in routine vertebral biopsies likely justifies the additional procedural expense, particularly when applied at the population level [2,6,15]. A comparable principle underlies screening colonoscopy: although only a minority of procedures detect advanced neoplasia, the practice is broadly endorsed because early detection and removal of precancerous lesions avert the far greater clinical and economic burden of colorectal cancer [39,40]. Despite these advantages, guideline recommendations remain conservative. The American College of Radiology (ACR) Appropriateness Criteria endorse biopsy

only when suspicion persists despite advanced imaging [41], whereas some Asian centers advocate for more liberal or even routine biopsy protocols [7,8]. European practice patterns fall between these extremes, reflecting uncertainty about cost–benefit balance [9,14]. Our findings challenge the adequacy of a purely selective approach: although small in absolute terms, the 3% prevalence of unsuspected malignancy in routine cohorts translates into a large absolute number of missed diagnoses worldwide [2,15,20,22]. Broader biopsy strategies may therefore be warranted, particularly in elderly, comorbid populations where the consequences of missed diagnoses are severe [4,13]. In addition to direct healthcare expenditures, the societal burden of missed or delayed diagnoses is considerable. Families often face increased caregiver responsibilities, loss of work productivity, and psychosocial stress when malignancies present late with neurological decline [32–34,38]. Early biopsy diagnosis, by enabling earlier initiation of appropriate care, may reduce these secondary costs [6,28]. Health economic models in osteoporosis management already recognize the cost of vertebral fracture morbidity [1]; incorporating malignancy detection into these frameworks would likely strengthen the argument for opportunistic biopsy [6].

4.7. Future Perspectives

Future research should extend beyond prevalence to patient-centered outcomes. Critical questions remain: did biopsy-detected malignancies lead to curative or palliative treatment, and how did diagnosis affect progression-free survival or quality of life? In an elderly, multimorbid population, patient preferences regarding diagnostic escalation and cancer therapy also require systematic evaluation. Biopsy discussions should therefore be multidisciplinary, involving oncologists and spine surgeons, and should explicitly include the patient's perspective. Furthermore, developing a practical scoring system that integrates age, comorbidities, imaging, and oncologic history could guide biopsy eligibility. Such a tool would complement existing prognostic frameworks such as the Tokuhashi, Tomita, and Van der Linden scores [42,43]. In addition, future health economic research should aim to quantify the comparative costs of selective versus opportunistic biopsy strategies, incorporating not only procedural and hospitalization costs but also indirect outcomes such as quality-adjusted life years (QALYs) and caregiver burden [6,28,34]. Such analyses would provide the evidence base necessary for international guideline harmonization and policy reform.

Limitations of this evidence must be acknowledged. Most included studies were retrospective and potentially subject to selection bias, since patients undergoing biopsy may have been enriched for higher baseline malignancy risk, inflating prevalence estimates. Variation in imaging protocols, diagnostic thresholds, and patient selection also limits generalizability. Nevertheless, this review benefits from comprehensive synthesis across malignancy types, large pooled cohorts, and robust heterogeneity assessments, including I^2 statistics, which improve transparency and reliability.

5. Conclusions

This meta-analysis demonstrates that vertebral biopsy is both safe and diagnostically valuable in the evaluation of vertebral compression fractures. Diagnostic yield varies markedly with patient selection—ranging from one in 30 in routine presumed benign fractures to nearly two in five in radiologic or clinical suspects and up to one in two in patients with both a history of malignancy and radiologic suspicion. These findings underscore the importance of integrating biopsy as both an opportunistic safeguard in routine cases and a high-yield diagnostic tool in selected high-risk populations. A structured, patient-centered strategy may enable earlier cancer detection, optimize management, and ensure appropriate oncologic referral.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/osteology5040030/s1, Table S1: PRISMA checklist. Reference [16] is citied in the Supplementary Materials.

Author Contributions: Conceptualization, H.B. and C.T.; methodology, H.B.; software, H.B.; validation, H.B.; formal analysis, H.B.; investigation, C.L.; resources, C.L., I.A. and V.S.; data curation, V.S.; writing—original draft preparation, H.B., C.L., V.S. and I.A.; writing—review and editing, C.T., K.O., A.H., C.E., R.B. and M.J.; visualization, H.B. and C.L.; supervision, K.O.; project administration, K.O.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: No animal or human subjects or sensitive data were used in this study; therefore, IRB approval was not deemed necessary. The protocol for this systematic review and meta-analysis has been registered with PROSPERO.

Informed Consent Statement: No patients or healthy subjects have been recruited for or participated in this study, evidence presented has been previously published in separate studies, thus no informed consent statement was distributed and collected.

Data Availability Statement: No primary data has been generated in the context of this study.

Conflicts of Interest: The authors declare no conflicts of interest.

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