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Systematic Review / Meta-Analysis

# Wide variability of the definitions used for native vertebral osteomyelitis: walking the path for a unified diagnostic framework with a meta-epidemiological approach

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**Abstract**

**BACKGROUND CONTEXT:** Native Vertebral Osteomyelitis (NVO) has seen a rise in incidence, yet clinical outcomes remain poor with high relapse rates and significant long-term sequelae. The 2015 IDSA Clinical Practice Guidelines initiated a surge in scholarly activity on NVO, revealing a patchwork of definitions and numerous synonyms used interchangeably for this syndrome.

**PURPOSE:** To systematically summarize these definitions, evaluate their content, distribution over time, and thematic clustering.

**STUDY DESIGN/SETTING:** Meta-epidemiological study with a systematic review of definitions.

**PATIENTS SAMPLE:** An extensive search of multiple databases was conducted, targeting trials and cohort studies dating from 2005 to present, providing a definition for NVO and its synonyms.

**OUTCOME MEASURES:** Analysis of the diagnostic criteria that composed the definitions and the breaking up of the definitions in the possible combinations of diagnostic criteria.

**METHODS:** We pursued a thematic synthesis of the published definitions with Boolean logic, yielding single or multiple definitions per included study. Using 8 predefined diagnostic criteria, we standardized definitions, focusing on the minimum necessary combinations used. Definition components were visualized using Sankey diagrams.

**RESULTS:** The literature search identified 8,460 references, leading to 171 studies reporting on 21,963 patients. Of these, 91.2% were retrospective, 7.6% prospective, and 1.2% RCTs. Most definitions originated from authors, with 29.2% referencing sources. We identified 92 unique combinations of diagnostic criteria across the literature. Thirteen main patterns emerged, with the most

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common being clinical features with imaging, followed by clinical features combined with imaging and microbiology, and lastly, imaging paired with microbiology.
**CONCLUSIONS:** Our findings underscore the need for a collaborative effort to develop standardized diagnostic criteria. We advocate for a future Delphi consensus among experts to establish a unified diagnostic framework for NVO, emphasizing the core components of clinical features and MRI while incorporating microbiological and histopathological insights to improve both patient outcomes and research advancements. 

*Keywords:* Consensus; Diagnosis; Diagnostic techniques; Discitis; Osteomyelitis; Spinal diseases; Systematic review

## Introduction

Native Vertebral Osteomyelitis is increasing in incidence in recent years [1], while clinical outcomes remain poor, given the high rate of relapses in approximately 15% to 31% of the patients [2] and long-term sequelae in a similar proportion of cases [3,4], bound with a deleterious impact on patients' ability to return to work [5,6]. Since the conceptualization of the 2015 IDSA Clinical Practice Guidelines [7] started in 2011, a significant increase in scholarly output in NVO provided a patchwork of definitions and a long enumeration of synonyms that are interchangeably used to describe the same syndrome [8].

Identifying gaps in evidence is crucial for both patient care and research advancement in the subsequent steps of defining and developing diagnostic criteria [9,10]. Previous eminent examples such infective endocarditis and prosthetic joint infections, with whom NVO shares many common host and pathogen features, natural history, clinical management, and diagnostic advances, already underwent this process with recent revisions [11,12] and external validations [13−15].

Meta-epidemiological studies, and especially systematic reviews of definitions, can be used in infectious diseases [16−18] or in other areas of medical research [19−23] to summarize and describe the distribution of available evidence, examine heterogeneity and explore its causes or biases, provide a framework for future advances, and inform subsequent international consensus on standardized and universally accepted definitions and diagnostic criteria in conditions where those are lacking [24−26]. Therefore, the aim of our study is to systematically summarize the definitions used for NVO and its synonyms across the available literature, to describe and evaluate their content and distribution across time and thematic clustering, focusing on the possible combinations of criteria used for diagnosis and underlining the importance of improvement of both patient care and scientific advancement.

## Methods

This meta-epidemiological study and systematic review was conducted and reported in accordance with the modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-epidemiological methodology research [26].

### *Protocol*

An *a priori* protocol was developed. The study protocol is available from the first and/or corresponding author on request.

### *Eligibility criteria*

We included studies that reported on at least fifty adults with NVO and/or its synonyms that provided a clearly recognizable and quotable definition of NVO and/or its synonyms in the manuscript or in the supplementary appendix. purposes. The minimum number of patients was selected arbitrarily in an attempt to improve generalizability, indirectly filter out studies with lower methodological rigor and design, and make the systematic review more feasible and focused. Detailed inclusion and exclusion criteria are outlined in the Supplementary materials. The primary outcome was the analysis of the diagnostic criteria that composed the definition and the breaking up of the definition in the possible combinations of criteria chosen *a priori*, assessing distribution across time and thematic clustering. The secondary outcome was the analysis of a subset of items thematically linked to the diagnostic criteria.

### *Information sources and search strategies*

A comprehensive search of several databases was performed on September 27, 2023. Results were limited to trials and cohort studies and by date from 2005 onward. The start date was chosen because it marked the beginning of the implementation of molecular diagnostic methods for NVO into clinical practice. Databases searched were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), and Scopus via Elsevier (1970+).

The search strategies were designed and conducted by an experienced medical librarian with input from the study investigators. They used controlled vocabulary supplemented with keywords. The actual strategy, listing all

search terms used and how they are combined, is available in the Supplemental material.

*Study selection*

The abstract and full-text screening was managed through the Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia). Two reviewers (FP, OKM) were involved in abstract and full-text screening. Each article was reviewed by 2 reviewers. To resolve any emerging disagreements, a third reviewer was consulted and/or consensus through discussion between the reviewers was achieved. Inter-rater reliability is shown in the Supplementary Appendix.

*Data extraction*

We piloted a data extraction form in REDCap on a sample of fifty manuscripts. Three reviewers (FP, OKM, and SEZ) piloted the form. Furthermore, based on the research team's advice, the form was further refined. Thus, in an iterative process between the reviewers, the form was modified to avoid misunderstandings or later disagreements. After this process, 2 independent reviewers (alternatively FP, OKM, or SMAA) extracted relevant information from each article and recorded it in separate REDCap and/or Excel sheets. Risk of bias assessment was not deemed relevant to this analysis which did not aim to estimate an association.

*Data synthesis and analysis*

We described data using counts and percentages. Extracted data are shown in the Supplementary Appendix. We pursued thematic synthesis of the definitions using the Boolean operators (AND, OR, AND NOT). Consequently, a single definition could, therefore, yield multiple outputs definitions if multiple possibilities were given by the authors for each study.

Eight *a priori*-defined individual criteria for diagnosis of NVO were used for standardizing the panorama of definitions based on widely available clinical practice and previous framework proposal from the same investigators [8]: (1) clinical features (symptoms, signs, patient's history), (2) inflammatory biomarkers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], white blood cell count [WBC]), imaging divided into (3) magnetic resonance imaging (MRI) and (4) other techniques (such as plain film X-rays, nuclear imaging, and computed tomography [CT] scans), microbiologic evidence from (5) blood cultures and (6) invasive techniques (including percutaneous or open spinal biopsy), (7) histopathology, and (8) empirical evidence of improvement following the initiation of antimicrobial therapy.

The theoretical sum of all possible combinations from a set of 8 categories without repetition was calculated using Pascal's triangle. The minimum possible combinations were then summarized using a saturation method that consisted of new combinations from definitions added to the list until no new combinations were identified. We decided to summarize only the minimum combinations offered by the single authors' definitions and not the total number of possible combinations, aiming at maximal clinical utility and according to the principle of parsimony—assuming that a clinician would use a specific definition for a definitive diagnosis of NVO if this proposes more options among the individual criteria, we chose the most elementary combination instead of all the possible combination from the definition provided. Individual criteria could be used alone to provide a definition, aiming at reproducibility.

To graphically depict the outcomes of this study, we utilized multidimensional analytics with a Sankey diagram to represent combinations derived from the definitions [27,28], weighting their distribution across the literature for the number of patients with NVO and its synonyms for each study. We utilize Microsoft Excel, High-D (Version 9.0; Macrofocus GmbH, 2019), and SankeyMATIC (https://sankeymatic.com/) as data analysis softwares.

## Results

The literature search yielded 8,460 references, of which 171 were finally included, covering 21,963 patients with the mentioned syndrome. The study selection process is depicted in Fig. 1 and Supplementary Table S6. The characteristics and bibliography of the studies included can be found in the Supplementary Appendix (Tables S4 and S5). Most definitions were described in retrospective observational studies (156/171, 91.2%). The remaining were in prospective studies (13/171, 7.6%), and randomized controlled trials (RCTs) (2/171, 1.2%). Most of these definitions were author derived (121/171, 70.8%). In the remaining articles, 4 publications were cited the most as a source of definition [7,29–31]. A minority of the studies (13/171, 7.6%) provided a score or classification applied to the proposed definition, with the most common being a distinction between definitive/probable/possible or presumptive diagnosis (11/13, 84.6%). One study each provided a classification based on *acute/subacute/chronic* criteria [32] or a previously validated classification [33].

*Diagnostic criteria*

The 3 most used diagnostic criteria were MRI (157/171, 91.8%), clinical features (124/171, 72.5%), and other imaging techniques (118/171, 69%), while the least 2 were histopathology (46/171, 26.9%), and empirical evidence of improvement following the initiation of antimicrobial therapy (21/171, 12.3%) (Fig. 2). Thirty-four of the 171 definitions (18.7%) allowed NVO to be defined using an individual diagnostic criterion, with histopathology alone being sufficient in 13/171 (7.6%) of the cases. According to the distribution of diagnostic criteria stratified by year of publication (Fig. 3), a spike in scientific production was

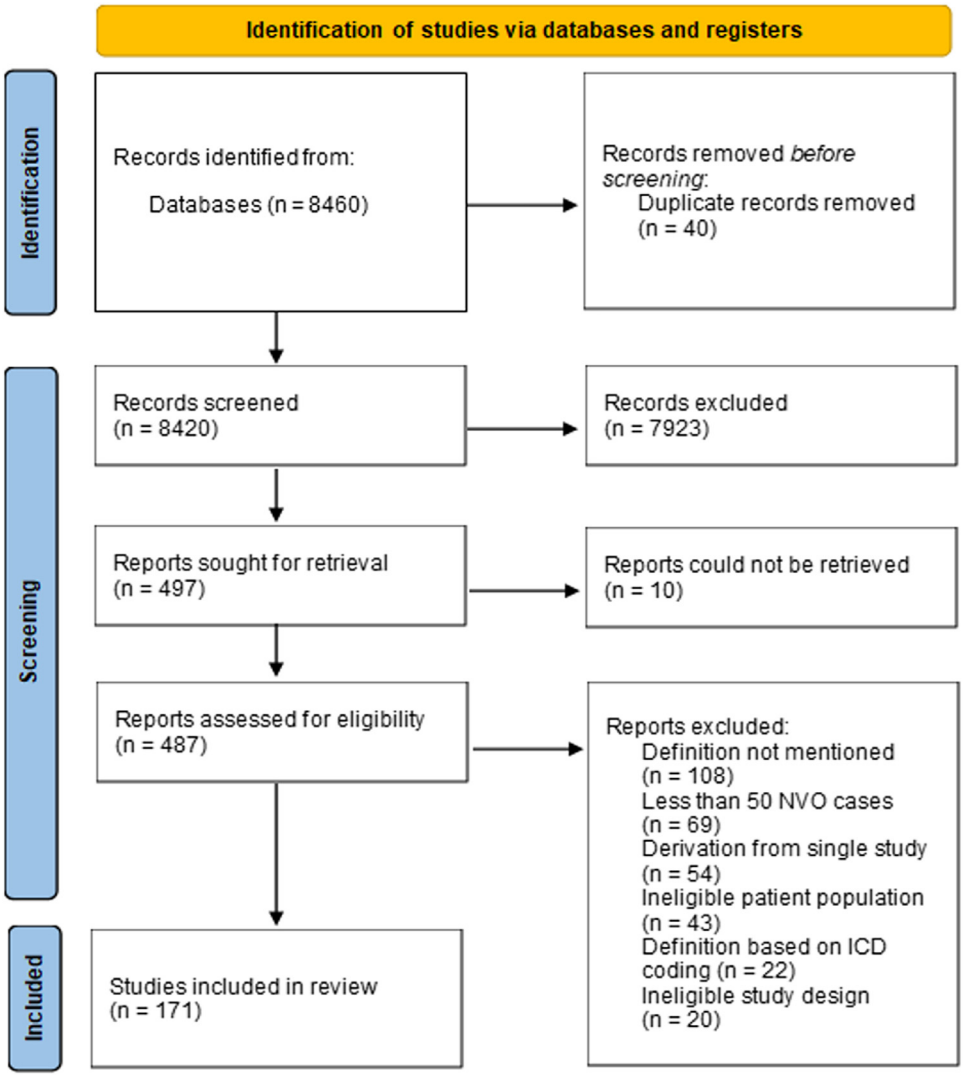


Fig. 1. 2020 PRISMA flow diagram.

seen in the years just before publishing the 2015 IDSA guidelines. Subsequently, a growing number of studies were published. Particularly, in most recent years, MRI and histopathology have been increasingly used across literature, while clinical benefits from empirical therapy did not increase at the same pace.

*Clinical features*

Information about specific symptoms or signs was available for 56/171 (32.7%) studies. Information regarding back pain was collected in 51/56 (91.1%) studies, fever in 45/56 (80.4%), neurological deficit in 27/56 (48.2%), limb pain in 7/56 (8.9%), chills in 3/56 (5.4%), weight loss and anorexia in 2/56 (3.6%), sepsis in 1/56 (1.8%), and other symptoms in 9/56 (16%).

When patient risk factors [7] were collected, the presence of diabetes mellitus was investigated in 116/171 (67.8%) studies, chronic kidney disease in 85/171 (49.7%), malignancy in 82/171 (47.9%), immunosuppression in 69/171 (40.3%), liver disease in 63/171 (36.8%), drug injection in 49/171 (28.6%), cerebrovascular, cardiac or peripheral artery disease in 47/171 (27.5%), postsurgical or prior spinal surgery/injection procedures in 41/171 (24%), rheumatological condition in 36/171 (21%), chronic pulmonary disease in 21/171 (12.3%).

For 52/171 (30.4%) information about the identification of a source of infection was provided. Urinary tract infection (UTI) was mentioned as a potential portal of entry for NVO causative pathogens in 35/52 (67.3%) studies, skin and soft tissue infection (SSTI) in 26/52 (50%), infective endocarditis in 20/52 (38.5%), lower tract respiratory infection (LRTI) in 17/52 (32.7%), catheter-associated bloodstream infection (CLABSI) in 16/52 (30.8%), bloodstream infection (BSI) in 15/52 (28.8%), other osteoarticular infection (OAI) in 8/52 (15.4%), central nervous system (CNS) infection in 1/52 (1.9%), other site in 40/52 (76.9%),

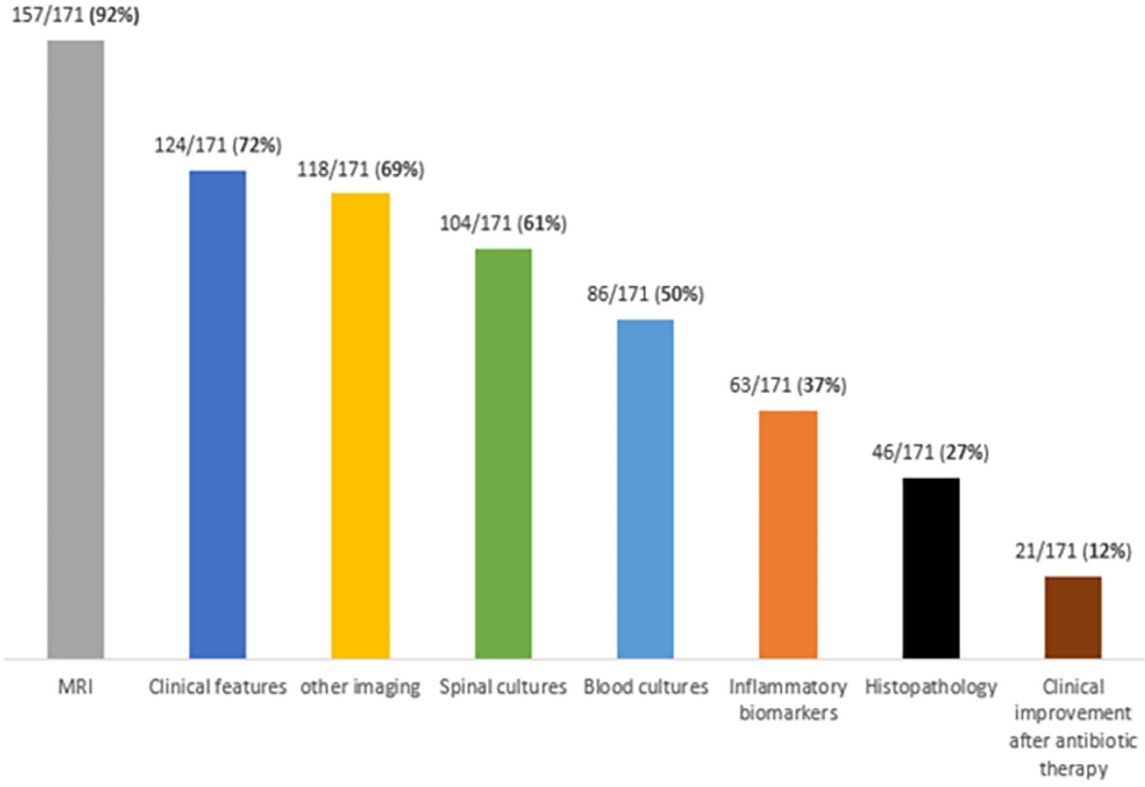


Fig. 2. Individual diagnostic criteria used by the authors for diagnosing NVO.

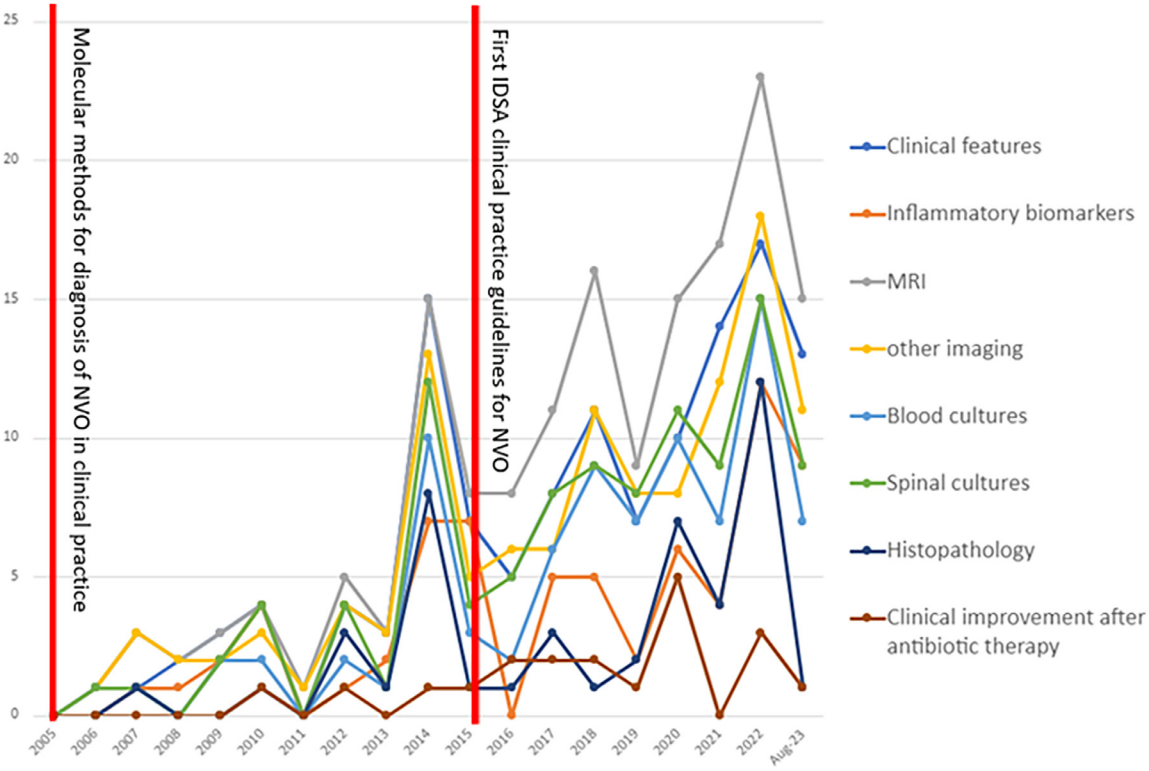


Fig. 3. Distribution of individual criteria according to year of publication.

especially abdominal, odontogenic, genital or after invasive procedure in any part of the body. A criterion for the exclusion of alternative diagnosis was provided in 26/171 (15.2%) studies.

*Inflammatory biomarkers*

WBC count was mentioned for diagnosis in 27/171 (15.8%) studies, CRP in 45/171 (26.3%), ESR in 27/171 (15.8%), other, e.g. anemia and procalcitonin (PCT) in 2/171 (1.2%).

*Imaging*

The use of MRI for diagnosis, alone or adjunctively, was explicitly mentioned in 149/171 (87.1%) studies, CT scans in 81/171 (47.4%), nuclear medicine with 99mTc SPECT (13/171, %), 67Ga SPECT (9/171, %), PET/CT (20/171, 11.7%), and plain films X-rays in 32/171 (18.7%) studies. 55/171 (32.2%) studies had detailed criteria for diagnostic imaging.

*Microbiology and histopathology*

Out of 171 studies, 122 (71.3%) included culture-negative cases. Specific definitions of culture-negativity were considered too variable to categorize. Apart from conventional cultures and histopathology, molecular techniques were used alone or adjunctively for diagnosis in 16/171 (9.4%) studies. Detailed histopathological criteria were available in 10/171 (5.8%) studies.

*Combinations of diagnostic criteria*

Out of the possible combinations from a set of 8 categories without repetition, 92/255 (37.2%) unique combinations of criteria for defining NVO and its synonyms were identified. A total of 526 definition options were retrieved. One article contributed 10 out of 92 (10.9%) possible definitions. Additionally, of the 171 articles, 5 provided 8 out of 92 (8.7%) definitions, twelve provided 6 out of 92 (6.5%), 6 provided 5 out of 92 (5.4%), forty-five provided 4 out of 92 (4.3%), eighteen provided 3 out of 92 (3.3%), fifty-six provided 2 out of 92 (2.2%), and twenty-eight provided 1 out of 92 (1.1%) definitions.

Analyzing the full set of possible options for definitions retrieved, the first twenty combinations were reported by at least ten papers (Table 1), accounting for 363/526 (69%) of the total definition options.

After grouping similar categories into semantically higher ones (e.g. MRI and other imaging) for a better depiction of clustering, we found thirteen prevalent patterns of combinations (Fig. 4), with the top 3 being:

1. Clinical features and imaging.
2. Clinical features, imaging and microbiology.
3. Imaging and microbiology.

The clustering of all ninety-two combinations shown by the complete Sankey diagram is available at Mendeley data [34].

Table 1
Twenty most common combinations of diagnostic criteria that were utilized by at least ten articles for diagnosing NVO

| Combinations of diagnostic criteria for NVO | Number of articles allowing the combination |
|---|---|
| Clinical features and MRI | 35 |
| Clinical features and other imaging | 27 |
| Clinical features and MRI and blood cultures | 25 |
| Clinical features and inflammatory biomarkers and MRI | 24 |
| Clinical features and MRI and spinal cultures* | 24 |
| MRI and spinal cultures* | 21 |
| Clinical features and other imaging and blood cultures | 21 |
| Clinical features and inflammatory biomarkers and other imaging | 20 |
| Clinical features and other imaging and spinal cultures* | 19 |
| MRI and blood cultures | 17 |
| Clinical features and inflammatory biomarkers and MRI and spinal cultures* | 15 |
| MRI | 15 |
| Clinical features and spinal cultures* | 15 |
| Spinal cultures* | 14 |
| Clinical features and inflammatory biomarkers and MRI and blood cultures | 13 |
| Other imaging and spinal cultures* | 13 |
| Histopathology | 13 |
| Other imaging and blood cultures | 11 |
| Clinical features and inflammatory biomarkers and other imaging and spinal cultures* | 11 |
| Clinical features and blood cultures | 10 |

* Considering only microbiology data from invasive biopsy of spinal tissue. Histopathology was considered as a separate category.

## Discussion

This is the first study of its kind in the field of NVO to systematically summarize the definitions used for its diagnosis in the available literature. We described and evaluated their content and distribution across time and thematic clustering, breaking down the possible combinations of diagnostic criteria, aiming to improve patient care and scientific advancement.

To the best of our knowledge, we found only one other systematic review of definitions concerning bone and joint infections (BJIs), specifically addressing infections after fracture fixation (IAFF) [16]. Their results align with ours, underlining the absence of a uniform definition of IAFF. Another study attempted to review the classification systems for pyogenic spondylodiscitis but did not specifically address definitions and employed a methodology different from ours [35].

We described ninety-two unique possible combinations of the 8 proposed diagnostic criteria used across the available literature to define NVO and its synonyms. This extreme variability shows the complexity of defining this syndrome and the need for higher quality evidence and collaborative research effort, as shown by the fact that only

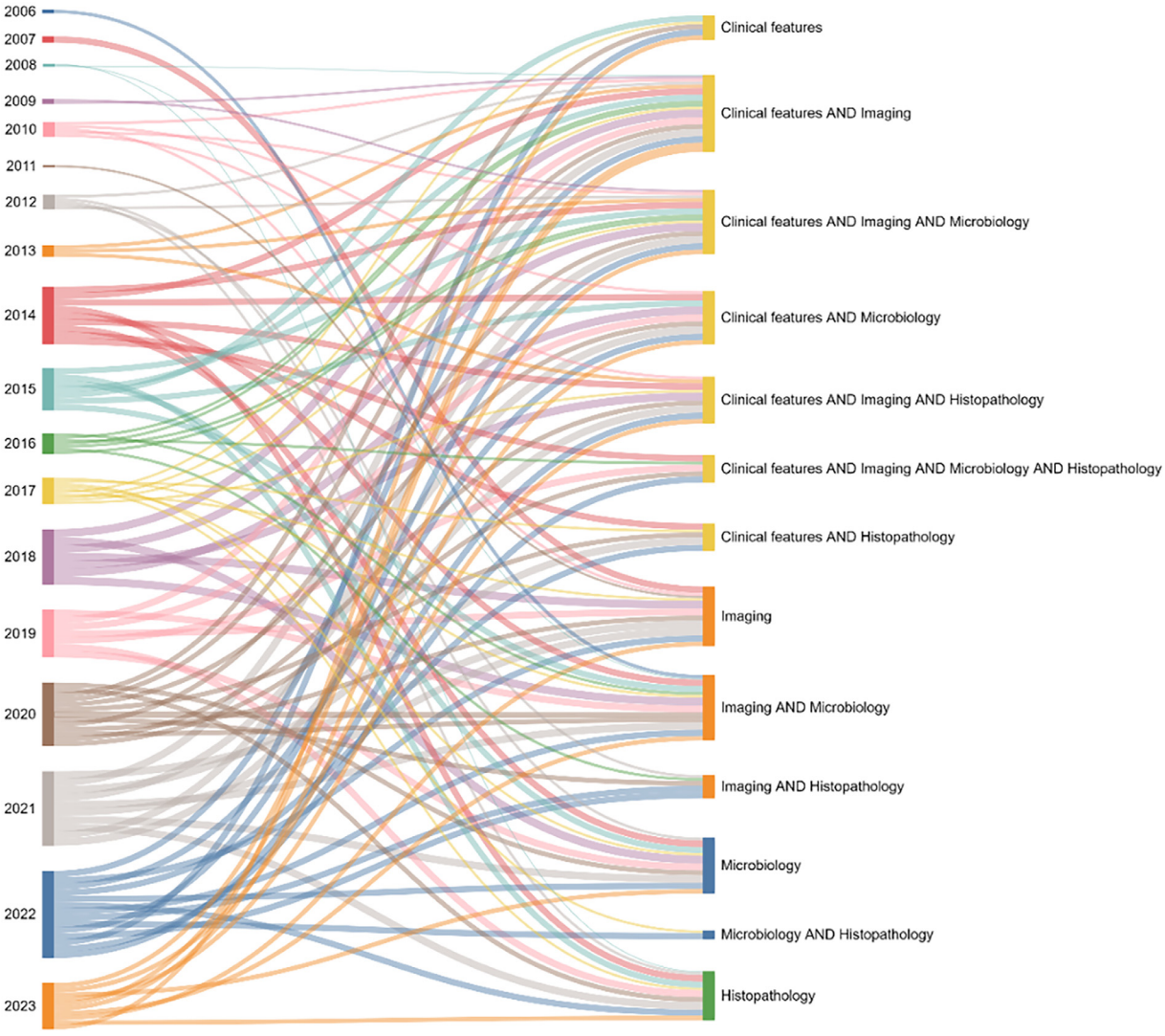


Fig. 4. Sankey diagram showing the distribution of combinations of diagnostic criteria for diagnosing NVO according per year of publication.

2 RCTs were evaluated in the present review for this rare, although increasingly diagnosed condition. This is underlined by the fact that no standard reference for definition was cited by the included studies, which mainly relied on the 2015 IDSA Clinical Practice Guidelines, which, however, do not report a definition. Moreover, the Centers for Disease Control and Prevention (CDC) provided a definition for disc space infection that applies to postsurgical cases. However, this definition does not cover infections in nonsurgical patients such as those with hematogenous seeding [36].

The lack of a unique noninvasive diagnostic test for NVO presents a challenge, as this condition is characterized by a wide range of potential differential diagnoses that must be excluded. However, the rarity of NVO makes it difficult to conduct randomized controlled trials (RCTs) with sufficiently large patient populations. Decision, whether to proceed with surgery such as corpectomy or conservative management alone, can pose significant challenges to the treating physician [37,38]. Moreover, if undiagnosed or left untreated, this condition nearly inevitably results in poor outcomes. A consensus on a common definition is, therefore, paramount. We observed that the evidence was generally of low quality, with most studies having small sample sizes. Only a few studies cited a publication, and many had to be excluded due to the risk of duplicating patient numbers, a common result of duplicate and salami publication practices. Both practices are harmful to science and society, as they can lead to copyright violations, distortion of scientific evidence, and misguidance of professionals and

policymakers. They also contribute to a problematic academic culture that favors quantity over quality in publications, create unfair competition, and burden those involved in the publication and funding of research with existing gaps in journal policies [39].

If we literally apply the definitions provided, for nearly 20% of the definitions included, a unique individual diagnostic criterion might suffice for NVO diagnosis. Nearly 8% of the papers used histopathology alone for NVO diagnosis (Table 1). However, traditionally, NVO diagnosis can be confirmed only if a combination of features is present [7,40]. Moreover, unlike histopathologic criteria for infective endocarditis, where the entire valve can be resected, needle or open biopsies for osteomyelitis might not target the affected area, leading to potentially false-negative results. Furthermore, the impact of treatment on histopathology is not fully understood, as treated NVO may exhibit features of chronic NVO. Therefore, differentiating solely based on histopathology—or based on just 1 criterion—can be extremely difficult without considering the full clinical context and it is not a recommended approach. Preliminary evidence suggests that differential analysis of disc space fluid may serve as a useful diagnostic tool for NVO. If validated in future studies, this method, when combined with other markers of NVO as an additional tool, could potentially establish the diagnosis in ambiguous cases [41,42].

Isolating the culprit pathogen can significantly impact patient outcomes, and every effort should be made to achieve this. Although we found that some authors accepted clinical features and imaging as criteria for defining NVO without using microbiological data—a practice not uncommon in a considerable proportion of cases—we also demonstrated in Fig. 3 that this practice has been declining in recent years. This trend is illustrated by the flattening of the curve representing the use of empirical benefits after antimicrobial treatment as a criterion, underscoring the need to minimize the proportion of culture-negative cases.

Future efforts should focus on improving diagnostic safety and availability, increasing feasibility, maximizing cost-benefit ratio, and further establishing the role of novel diagnostic techniques such as molecular tests and disc space fluid differential counts for NVO diagnosis. Moreover, the performance of diagnostic criteria beyond clinical assessment, such as imaging coupled with microbiology, warrants further investigation especially in cases of asymptomatic embolization from other infectious foci, such as infective endocarditis or bloodstream infections. PET/CT has shown promising results in these settings [43]. Therefore, establishing a unified definition of NVO is crucial to enhancing research quality, comparability, and patient outcomes.

### *Limitations*

Our study has some limitations. First, including only articles with a preset number of patients with NVO and its synonyms might have introduced selection bias. This criterion was chosen for feasibility purposes, and given the high number of articles screened, we believe that wide coverage of different situations was still addressed, especially considering the extensive search strategy provided by an experienced librarian at our institution. However, the arbitrary selection of fifty patients may still limit the generalizability of our findings. This threshold, while practical, may exclude potentially relevant studies with smaller patient cohorts. We encourage future research to explore a broader range of sample sizes and highlight the importance to keep the systematic review regularly updated [44]. We acknowledge the potential temporal bias due to the 2005 date limitation and the possibility of missing relevant studies if different terminologies on NVO were used [8]. However, we selected 2005 because this is when PCR and molecular methods became widely adopted for diagnosing bone and joint infections [45], ensuring that our review reflects contemporary practices. To further mitigate the risk of missing relevant studies, we based our search strategy on multiple piloted simulations to accommodate various terminologies, aiming for both comprehensiveness and feasibility. Second, we might have misinterpreted some definitions since wide variability was also shown for inclusion and exclusion criteria, and the purposes of the studies were greatly different. However, we think that applying our methodology consistently to every study might add comparability and stronger conclusions. Third, the application of the principle of parsimony might overrepresent the instances where a single diagnostic criterion was used exclusively for diagnosis. However, clinicians might be conscious that a combination of criteria must be used for diagnosis and consistently already apply this in real-world. This simplification was done to ensure reproducibility. For transparency purposes, all the data collected, and the detail of the combinations "*in vitro*" built from definitions can be found in Supplementary Table S5. Finally, since the vast majority of studies were of low quality of evidence, and due to the variability of definitions used, we could not provide a suggested definition, but the prevalent patterns encountered will be used as a foundation framework for a future Delphi consensus among experts.

## Conclusions

In conclusion, we showed there is significant heterogeneity among the definitions used for NVO and its synonyms, and higher-quality evidence is needed. Clinical features and MRI should still be core components of this diagnostic framework, but greater microbiological and histopathological insights are needed.

## Declaration of competing interest

One or more of the authors declare financial or professional relationships on ICMJE-TSJ disclosure forms.

## CRediT authorship contribution statement

**Francesco Petri:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Omar K. Mahmoud:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Said El Zein:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Seyed Mohammad Amin Alavi:** Writing – review & editing, Data curation, Conceptualization. **Matteo Passerini:** Writing – review & editing, Writing – original draft, Conceptualization. **Felix E. Diehn:** Writing – review & editing, Supervision, Conceptualization. **Jared T. Verdoorn:** Writing – review & editing, Supervision, Conceptualization. **Aaron J. Tande:** Writing – review & editing, Supervision, Conceptualization. **Ahmad Nassr:** Writing – review & editing, Supervision, Conceptualization. **Brett A. Freedman:** Writing – review & editing, Supervision, Conceptualization. **M. Hassan Murad:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Elie F. Berbari:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

## Access to data

The full dataset is available through the first and corresponding authors upon a reasonable request.

## Data statement

This study was previously presented at: ESCMID Global; April 27–30, 2024; Barcelona, Spain.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2024.09.018.

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