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Raman spectroscopy as a diagnostic tool for glioma: protocol for a systematic review

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Abstract

Background Glioma is the most common primary brain tumor, demanding prompt and accurate diagnosis to guide therapy decisions. Conventional diagnostic methods such as histopathology and neuroimaging are limited by their invasiveness, subjectivity, or lack of intraoperative precision. Raman spectroscopy is an emerging, label-free optical technique that detects the unique molecular "fingerprint" of tissues, enabling real-time differentiation between tumor-infiltrated and normal brains based on their biochemical composition. Despite a growing body of experimental and translational studies, a comprehensive synthesis of Raman spectroscopy's clinical applicability in detecting glioma micro-infiltration is lacking.

Methods We will search four electronic databases (PubMed, Embase, Scopus, and Web of Science) for English-language studies published from 2015 to 2025. Eligible studies may use in vivo Raman (subjects with suspected or histologically confirmed glioma), ex vivo Raman (freshly excised human tissue), or in vitro analysis on archived human samples, provided the tissue originated from confirmed glioma cases. Primary outcomes will be diagnostic accuracy measures, including but not limited to sensitivity, specificity, accuracy, area under de curve (AUC), positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR), and positive/negative likelihood ratios (LR+/LR–). Secondary outcomes include its role in intraoperative margin assessment, diagnostic time, and machine learning-assisted classification. Data traction and risk of bias assessment will be conducted independently by two reviewers. Meta-analyses will be performed using specific statistics where applicable. If a meta-analysis is not feasible, a structured narrative synthesis will be employed, following the SWiM (Synthesis Without Meta-analysis) guidelines. GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) will be applied to evaluate the certainty of evidence. The review will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Discussion This review will synthesize the emerging diagnostic landscape of Raman spectroscopy for glioma, positioning it as a transformative adjunct to traditional histopathology and intraoperative decision-making. Our findings will pave the way for a translational roadmap to integrate real-time Raman spectroscopy into neurosurgical workflows with machine learning support.

Systematic review registration PROSPERO: CRD420251025922.

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Keywords Raman spectroscopy, Glioma, High-grade glioma, Brain neoplasms, Machine learning

Background

Glioma is the most common primary brain tumor, with an annual age-adjusted incidence rate of 6.0 per 100,000 population [1], representing the most common type of primary central system tumors [2, 3]. Currently, the standard treatment for malignant glioma is maximal safe surgical resection [4]. Previous studies have demonstrated that extending the resection could improve patients' diagnosis and provide conditions for subsequent therapy [5, 6]. However, high invasion of gliomas hampers the precise delineation of tumor margins during surgery so that residual malignant cells often remain and drive rapid postoperative recurrence [7]. Consequently, determining the tumor boundaries and equilibrium between the potential functional impairments caused by excessive resection and the risk of disease progression with insufficient resection is essential in glioma treatment [8].

Intraoperative diagnosis currently relies on histopathological assessment, which is considered the gold standard for diagnosis. However, despite its accuracy, combining histological and molecular features of glioma is time-consuming and limited in spatial coverage, raising the costs for patients [9]. Additionally, microscopic diagnosis requires the intervention of multiple experienced pathologists for the analysis of hematoxylin and eosin-stained slides [10]. Moreover, the need for invasive surgical resection or biopsy of glioma tissue, followed by Sanger sequencing [11] and fluorescence in situ hybridization (FISH) [12], complicates the diagnosis.

Accurate delineation of tumor margins to assist neurosurgeons in achieving complete resection has become a critical objective in neurosurgery. Imaging techniques have been dramatically helping surgeons to identify tumor boundaries and improve operation accuracy. Currently, imaging modalities such as magnetic resonance imaging (MRI), fluorescence-guided imaging, and positron emission tomography (PET) provide valuable intraoperative information [13]. Several studies demonstrated that a greater extent of tumor resection guided by contrast-enhanced MRI could extend the median overall survival of glioma patients [14–17]. PET complements traditional imaging modalities based on structure, providing valuable information regarding the processes involved in delineating and extending tumor boundaries [15, 17]. However, due to the lack of anatomical resolution necessary for precise tumor localization within the brain, PET is commonly paired with high-resolution anatomical imaging modalities, such as MRI [17]. Additionally, it is essential to acknowledge that none of these single imaging modalities is without limitations. Most imaging techniques target different markers or mechanisms, and their resolution is insufficient to detect micro-infiltrative tumor cells, which makes visualizing glioma margins a challenge with diverse implications [13].

Raman spectroscopy is an emerging, label-free optical technique that detects the unique molecular "fingerprint" of tissues, enabling real-time differentiation between tumor-infiltrated and normal brains based on their biochemical composition [18]. Recent studies have utilized Raman spectroscopy to demonstrate these differences at the cellular level [19–23], highlighting the potential of Raman spectroscopy to effectively delineate glioma boundaries. It has shown considerable promise in identifying biochemical changes associated with early-stage glioblastoma infiltration. Recent advances in laser technologies, fiber optics, and machine learning have further facilitated the integration of Raman spectroscopy into clinical workflows, enhancing its potential as a real-time diagnostic tool [24].

Despite a growing body of experimental and translational studies, a comprehensive synthesis of Raman spectroscopy's clinical applicability in detecting glioma micro-infiltration is lacking. This systematic review aims to critically evaluate current evidence on the diagnostic utility of Raman spectroscopy in glioma, with a focus on its intraoperative performance, methodological consistency, and translational readiness. Specifically, it will examine how effective Raman spectroscopy (Intervention), alone or in combination with machine learning techniques, is in diagnosing glioma among adult patients with suspected or histologically confirmed disease (Patients), compared to standard diagnostic modalities such as histopathology, intraoperative frozen section, MRI, fluorescence imaging, or PET (Comparators), in terms of diagnostic accuracy metrics (Outcomes). Secondary outcomes will explore its role in surgical margin assessment and intraoperative guidance.

Methods/design

This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [25] and for systematic review Protocols (PRISMA-P) [26]. Moreover, the study will adhere to the Synthesis Without Meta-analysis (SWiM) guidelines [27]. The protocol has been recorded in PROSPERO (CRD420251025922).

Eligibility criteria

The selection criteria will be described according to Patients, Intervention, Comparison and Outcomes (PICO) statements.

Patients

Inclusion criteria Studies must involve adult patients (aged ≥ 18 years) with suspected or histologically confirmed glioma, undergoing diagnostic evaluation, surgical intervention, or guided-tissue sampling for glioma using Raman spectroscopy. Studies involving mixed glioma populations will be considered if diagnostic performance data specific to glioma are reported separately or if most of the sample comprises glioma cases.

Exclusion Studies involving pediatric populations, non-human subjects, or glioma cell lines will be excluded. Studies where the patient population is not clearly described or where glioma-specific data cannot be extracted will also be excluded.

Intervention The use of Raman spectroscopy, either alone or combined with machine learning algorithms, as a diagnostic approach for the detection and characterization of glioma.

Comparison Raman spectroscopy will be compared against standard diagnostic modalities, including but not limited to intraoperative frozen section analysis, confirmed postoperative histopathology (diagnostic standard), magnetic resonance imaging, fluorescence imaging, and positron emission tomography.

Outcomes Primary outcomes will be diagnostic accuracy measures, including but not limited to sensitivity, specificity, accuracy, AUC, positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR), and positive/negative likelihood ratios (LR+/LR−). Secondary outcomes will explore its role in surgical margin assessment and intraoperative guidance.

Information sources

This systematic review will methodically explore electronic bibliographic databases. Specific keywords (e.g., glioma, Raman spectroscopy) will be searched in various databases including PubMed, Embase, Scopus, and Web of Science. The initial search will include English language studies published between January 2015 and the date of protocol registration. Before data extraction, a final search update will be conducted to ensure the most recent studies are included.

Search strategy

The search will be done in PubMed, Embase, Scopus, and Web of Science. The principal search keywords will be "Raman" and "glioma", and "diagnostic". The "Raman" keyword will be expanded to include relevant synonyms and variations to maximize search sensitivity: "Raman spectroscopy," "Raman spectrum," "Raman spectra," "Raman scattering," "Raman imaging," "Raman optical activity," "Raman signal," "Raman shift," "Raman-based technique," "Raman spectroscopic analysis," "Raman spectrometer," "Raman spectroscope." In the same way, the "glioma" term will be expanded to increase sensitivity: "glioma," "gliomas," "glioblastoma," "glioblastoma multiforme," "GBM," "grade IV glioma," "high-grade glioma," "HGG," "anaplastic astrocytoma," "grade III glioma," "astrocytoma," "malignant glioma," "diffuse glioma," "recurrent glioma," "progressive glioma," "glial tumor," "brain tumor," "brain tumor," "brain neoplasm," "central nervous system neoplasm," "CNS tumor." These two sets of terms will be combined using various Boolean operators ("OR" within each group and "AND" between the two groups) to ensure that search results reflected studies discussing both Raman spectroscopy and glioma or its equivalent terminology. These terms will be searched across databases using a controlled vocabulary (e.g., MeSH terms, where applicable) and free-text (title/abstract). The database searches will be split among team members, with each reviewer assigned specific databases to search using the exact predefined search terms and filters (C.O.V. will search into Embase and and Scopus; M.N. will search into PubMed and Web of Science). All search results will be combined and deduplicated in a reference manager (e.g., Zotero) before screening. The study will include papers published after January 2015 and before data extraction. For PubMed, the following draft search strategy will be used to identify studies related to glioma and Raman spectroscopy:

> ("Glioma"[MeSH] OR "Brain Neoplasms"[MeSH] OR glioma* OR glioblastoma OR "glioblastoma multiforme" OR GBM OR "high-grade glioma" OR HGG OR "grade IV glioma" OR "grade III glioma" OR "anaplastic astrocytoma" OR astrocytoma OR "malignant glioma" OR "diffuse glioma" OR "recurrent glioma" OR "progressive glioma" OR "glial tumor" OR "brain tumor" OR "brain tumour" OR "brain neoplasm" OR "CNS tumor" OR "central nervous system neoplasm")
> AND
> ("Raman Spectroscopy"[MeSH] OR "Raman spectroscopy" OR "Raman spectrum" OR "Raman spectra" OR "Raman scattering" OR "Raman imaging" OR "Raman signal" OR "Raman shift" OR "Raman-based technique" OR "Raman optical activity" OR "Raman spectroscopic analysis" OR "Raman spectrometer" OR "Raman spectroscope")

This strategy will be adapted for use in other electronic databases (e.g., Scopus, EMBASE, Web of Science). At this stage, search results will be limited to studies published in English between January 1, 2015, and date of

protocol registration (May 30, 2025), to ensure inclusion of recent and relevant research.

Study records

Data management

The literature search will be systematically conducted using a combination of keywords and controlled vocabulary (MeSH terms) to ensure a comprehensive and precise retrieval of relevant studies. The search strategy will include the application of date restrictions (e.g., limiting results to publications from 2015 to 2025) and language filters (e.g., restricting to studies published in English only) to align with the scope and feasibility of the review. All search results retrieved from the selected electronic databases will be imported into Zotero, an open-source reference management software. Zotero's built-in Duplicate Items tool, available in its desktop version, will be used to automatically detect and consolidate duplicate records, ensuring that each study is represented only once in the dataset. After the deduplication process is complete, the cleaned and unified reference list will be exported for the screening phase.

Selection process

Two independent reviewers will manually perform both title/abstract screening and full-text screening, according to predefined eligibility criteria. This structured approach facilitates transparency, reproducibility, and accuracy throughout the study selection process. The full texts of potentially eligible studies will be obtained and assessed in detail based on the eligibility criteria (excluded if: not about glioma or high-grade glioma, not using Raman spectroscopy, not original research, animal or cell line studies, conference abstracts without full text) and any discrepancies will be resolved by involving of a third reviewer. The number of discrepancies between reviewers at both title/abstract and full-text screening stages, as well as the proportion of records requiring resolution out of the total screened records, will be recorded. The inter-reviewer agreement will be reported using Cohen's kappa coefficient. Full texts of included studies will be retrieved through institutional access, open-access repositories, or by contacting authors. During this stage, reasons for exclusion will be documented systematically (e.g., not Raman, not glioma, not human, no diagnostic data, conference abstract only, lack of data regarding sensitivity, specificity, and accuracy). Preprints (unpublished studies without peer review) and retracted articles will be excluded. Only peer-reviewed, published articles available in scientific journals or indexed in the databases will be considered eligible. The review team will verify the publication status of all included studies and screen for retractions before data synthesis. Before data extraction, the final included studies will be verified for eligibility and completeness of reported diagnostic data. Subsequently, a PRISMA 2020 flow diagram will document the selection process (Fig. 1).

Data collection process

Two reviewers will independently extract data from each included study. A standardized extraction sheet will be used in Excel and will include study characteristics, population details, Raman spectroscopy details (e.g., type, wavelength, analysis method), comparator used, and diagnostic outcomes (e.g., sensitivity, specificity, AUC). Disagreements will be resolved by discussion or third-reviewer involvement.

Data items

For each included study, we will extract a set of variables and group them based on PICO definitions:

General characteristics of included studies

- publication year, journal, country of origin
- study design (prospective, retrospective, cross-sectional)
- sample size (total number and depending on the type of glioma)
- funding sources

Patients

- demographics (age, gender, glioma subtype)
- inclusion/exclusion criteria used in each study
- glioma confirmation—histopathology done/not done
- World Health Organization (WHO) glioma classification (II, III, IV) and tumor localization

Intervention

- Type of Raman spectroscopy (e.g., traditional Raman, SERS, handheld probe)
- sample type (in vivo, ex vivo, archived samples)
- wavelength(s), acquisition settings, preprocessing steps
- machine learning or statistical classifiers applied for the processing, feature extraction, dimensionality reduction, and classification of Raman spectral data (if any), including model type (e.g., principal component analysis (PCA), support vector machine (SVM), convolutional neural networks (CNN)).

Comparator

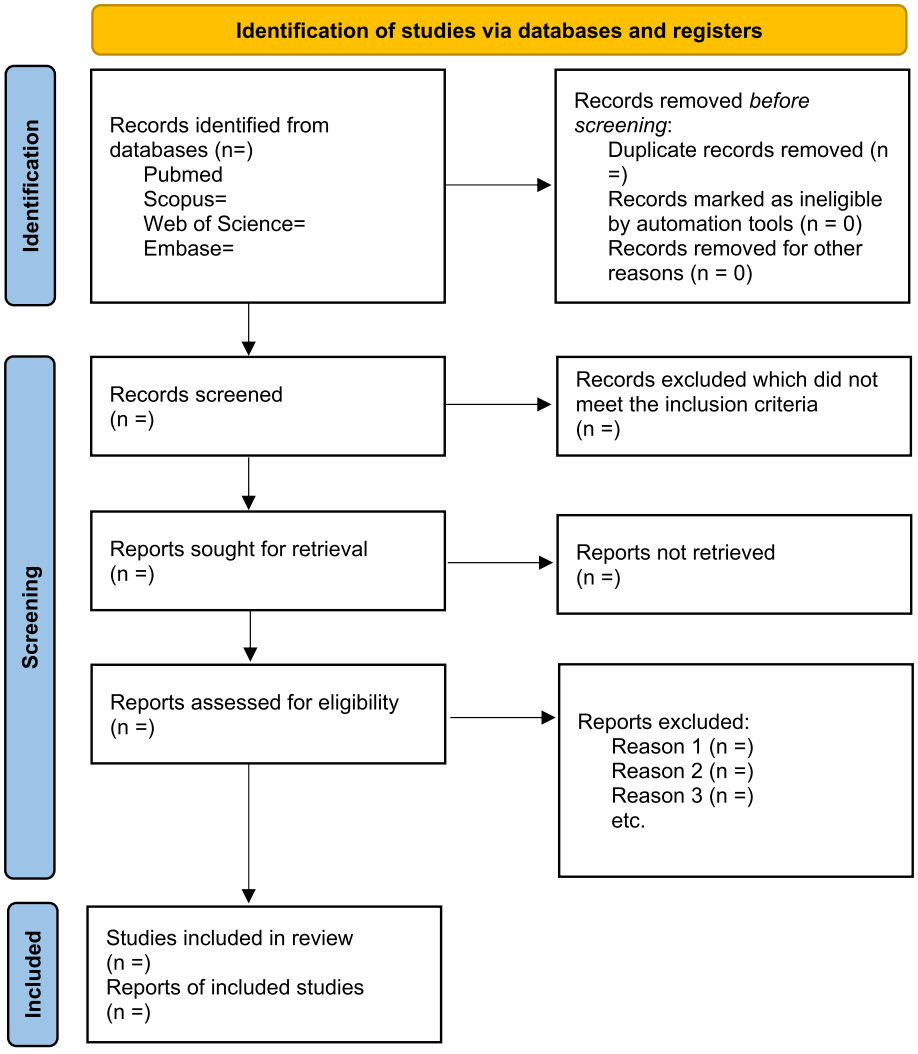

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection [25]

– type of diagnostic standard(s) used (e.g., histopathology, magnetic resonance imaging, positron emission tomography)

Outcomes

– diagnostic metrics, including sensitivity, specificity, accuracy, area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR), and positive and negative likelihood ratios (LR+ and LR−).
– Additional outcomes: margin assessment accuracy, intraoperative decision time, interpretability, and feasibility

Outcomes and prioritization

Primary outcomes

Primary outcomes will be diagnostic accuracy measures, including but not limited to sensitivity, specificity, accuracy, AUC, positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR), and positive/negative likelihood ratios (LR+/LR−). While not all studies may evaluate Raman spectroscopy against every comparator, the review will extract and synthesize available diagnostic performance data as reported in each study, with respect to the reference standard used.

Secondary outcomes

Secondary outcomes will explore its role in surgical margin assessment and intraoperative guidance. In addition, if data are available, the assessment would also examine outcomes encompassing speed of intraoperative decision-making or time to diagnosis, the contribution of machine learning techniques to diagnostic performance,

the feasibility of application in clinical settings, and diagnostic performance differences according to the sample type (in vivo versus ex vivo) or the location in the tissue (tumor core versus margins).

Risk of bias assessment

The risk of bias for all included diagnostic accuracy studies will be evaluated using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies – version 2), which is specifically designed to assess the internal validity of studies evaluating diagnostic performance. The tool covers four key domains: patient selection, index test, reference standard, and flow and timing. Each domain will be assessed for risk of bias and applicability concerns. Risk of bias assessments will be conducted by a single reviewer, who will apply the QUADAS-2 criteria consistently across all included studies. Any uncertainties or ambiguities encountered during assessment will be documented and, where necessary, discussed with a second reviewer for clarification. The results will be summarized in tabular form and accompanied by a narrative synthesis.

Data synthesis

The critical analysis of data from included studies will first include summarization in structured tables and narrative synthesis based on Raman type (in vivo vs. ex vivo), use of machine learning, sample size, and diagnostic outcomes. If 10 or more studies provide proportionate diagnostic values (e.g., sensitivity and specificity), a meta-analysis will be conducted using a bivariate random-effects model to generate pooled estimates, including sensitivity, specificity, diagnostic odds ratio (DOR), and the area under the summary receiver operating characteristic (SROC) curve, each with 95% confidence intervals. Statistical heterogeneity will be assessed using the I^2 statistic, alongside visual inspection of SROC curves and consideration of potential threshold effects, as recommended for diagnostic test accuracy meta-analyses. Subgroup analyses will be performed based on Raman modality (e.g., conventional, SERS), application context (intraoperative vs. laboratory), and whether machine learning was used. The potential influence of machine learning methodology, including preprocessing strategies and validation approaches, as well as sources of bias such as overfitting, lack of external validation, and data leakage, will be critically examined as contributors to heterogeneity. In addition, reported Raman spectral features and their proposed biochemical correlates (e.g., lipids, proteins, nucleic acids) will be systematically summarized and compared across studies, with particular attention to consistency and biological plausibility. If meta-analysis is not feasible, a structured narrative synthesis will be used following SWiM (Synthesis Without Meta-analysis) guidelines.

Meta-biases

To assess meta-biases, particularly publication bias and selective outcome reporting, a structured approach will be applied, adapted to the number of studies available for each outcome. When at least ten studies are included for a given outcome, publication bias will be evaluated both visually and statistically (funnel plots, Egger's regression test, trim and fill, small study effects). In situations where fewer than 10 studies are available, statistical tests for publication bias may not be reliable. In such cases, a narrative assessment will be conducted to explore potential sources of bias. This will involve examining factors such as study sample size, precision of estimates, funding sources (e.g., commercial versus independent), publication status (e.g., peer-reviewed versus grey literature), and the consistency of outcome reporting relative to study protocols or trial registrations. Particular attention will be given to detecting signs of selective reporting or interpretative spin in the presentation of findings. When appropriate, qualitative methods such as the ROB-ME (Risk of Bias due to Missing Evidence) framework, developed by Cochrane, will be consulted to assess the influence of missing data on the overall body of evidence. The outcomes of all meta-bias assessments, whether visual, statistical, or narrative, will be clearly documented and integrated into the interpretation of the systematic review's conclusions.

Confidence in cumulative evidence

The GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluations), including factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias, will be used to assess the certainty of evidence across studies for each outcome. Using GRADEpro GDT, a Summary of the Findings table will be created.

Discussion

Raman spectroscopy is an emerging, non-invasive optical technique providing critical insights regarding the chemical compositions and structural characteristics in the early stages of disease progression, serving as a promising tool to identify glioma micro-infiltration [18]. It has shown promise for identifying glioma in real time, particularly when combined with machine learning algorithms for spectral classification [24].

This systematic review aims to critically evaluate current evidence on the diagnostic utility of Raman spectroscopy in glioma, with a focus on its intraoperative performance, methodological consistency, and translational readiness. However, several operational and

practical considerations will influence this review. One concern is the heterogeneity of Raman systems (e.g., handheld vs. bench-top devices, variations in laser wavelengths), analysis methods (traditional statistical methods vs. neural networks), and sample types (in vivo, ex vivo, or archived tissues). These factors may introduce substantial variability in diagnostic accuracy estimates and affect comparability across studies. A further challenge is the lack of standardization in defining and reporting diagnostic metrics. Some studies may report only sensitivity/specificity, while others include AUC or likelihood ratios, and a subset may lack clear reference standards altogether. Consequently, a structured narrative synthesis may be required for studies that do not provide sufficient quantitative data for meta-analysis (Synthesis Without Meta-analysis). Additionally, the feasibility of intraoperative implementation, including time constraints, operator training, tissue preparation, and integration with surgical navigation, will be considered when interpreting translational readiness. While some studies explore real-time or label-free diagnostics, others remain proof-of-concept. Lastly, we acknowledge that Raman spectroscopy's clinical value will depend not only on diagnostic accuracy but also on usability, reproducibility, and cost-effectiveness, all of which are underreported in primary studies.

This review may provide a basis for standardizing methodology and prioritizing clinical translation in future trials. Importantly, it will map current evidence gaps such as the lack of prospective, multicenter trials, absence of standardization in Raman data acquisition and preprocessing, and limited regulatory pathways. These findings will not only contextualize Raman's potential as a real-time intraoperative adjunct but also outline a translational roadmap, highlighting next steps required for clinical adoption and regulatory approval. As such, the review aims to advance both evidence-based practice and future research agendas in neurosurgical oncology.

Abbreviations

AUC	Area under the curve
PPV	Positive predictive value
NPV	Negative predictive value
DOR	Diagnostic odds ratio
LR+/LR–	Positive/negative likelihood ratios
SWiM	Synthesis Without Meta-analysis
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
FISH	Fluorescence in situ hybridization
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PRISMA-P	Preferred Reporting Items for Systematic Reviews Protocols
PICO	Patients, Intervention, Comparison and Outcomes
MeSH	Medical Subject Headings
WHO	World Health Organization
PCA	Principal Component Analysis
SVM	Support Vector Machine
CNN	Convolutional Neural Network
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies – version 2
SROC	Summary receiver operating characteristic
ROB-ME	Risk of Bias due to Missing Evidence

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Authors' contributions
Conceptualization: COV, IP and MP. Data curation: MCC, BO, and AP. Investigation: COV, MN, EM, REC, and AS. Methodology: NS, IP, and COV. Project administration: COV and IP. Supervision: IP and MP. Validation: AP and MCC. Writing—original draft: COV, MN, and IP. Writing—review and editing: COV, BO, and IP. COV is the guarantor of the review.

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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