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Unveiling The Hidden Threat: Exploring the Diagnostic Prowess of MRI in Detecting Post-Laminar Optic Nerve Invasion in Retinoblastoma Patients - a Meta-Analysis

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ABSTRACT

Retinoblastoma (RB) is a rare, aggressive intraocular malignancy affecting the retina in children, with an incidence of about 1 in 15,000 live births worldwide. Preoperative magnetic resonance imaging (MRI) is increasingly used to detect post-laminar optic nerve invasion (PLONI), a key factor influencing treatment strategies. This meta-analysis aimed to evaluate MRI's diagnostic accuracy in detecting PLONI in retinoblastoma patients by focusing on sensitivity and specificity. Following PRISMA 2020 guidelines, a systematic search was performed in Google Scholar, PubMed, EBSCOhost, and ProQuest up to 2023. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Sensitivity and specificity data were extracted and pooled using STATA 17 for meta-analysis. Seventeen studies met eligibility criteria. The pooled results revealed an overall sensitivity of 69.0% (95% CI: 58%–80%) and specificity of 80.0% (95% CI: 73%–87%), with significant heterogeneity (I^2 = 85.5%). These findings suggest that MRI has high specificity for detecting PLONI in RB patients, making it a valuable tool, especially when considering eye-preserving treatments. Accurate preoperative identification of PLONI via MRI can critically guide clinical decisions and improve outcomes for children with retinoblastoma.

INTRODUCTION

Retinoblastoma (RB) is the most prevalent primary intraocular cancer in children, affecting around one in every 15,000 to 20,000 live births globally (de Jong et al., 2014). Because to the significant advancement of RB management and treatment choices, the survival rate in Western nations now surpasses 95%, whereas it stays between 40 and 80% in Asia and Africa (Dimaras et al., 2015). The most common cause of disease-related mortality in RB patients is distant metastases. The presence of post-laminar optic nerve invasion (PLONI) is a poor prognostic sign and is linked to an increased risk of local recurrence or systemic metastasis (Kaliki et al., 2013). Significant modifications in treatment regimens have occurred in recent years, with the increased adoption of eye-sparing therapy techniques (Fabian et al., 2018). Although eye-salvage treatment offers significant benefits in terms of patient care, the lack of histopathologic screening for the identification of risk factors makes deciding between

enucleation and eye-sparing treatment difficult. As a result, reliable preoperative PLONI information is critical for selecting surgical candidates among individuals considering eye-sparing treatment (Li et al., 2020).

The optic nerve invasion level has been categorised as prelaminar, laminar (intralaminar), post-laminar, and involving surgical margin based on the worldwide RB staging work group for histological analysis and globe production (Cho et al., 2021; Karim, Hasanuzzaman, Joya, & Islam, 2024; Liu et al., 2023). It has also been determined that choroidal invasion can be either focal or massive with a tumour with a diameter of 3 mm or more is considered to have a major choroidal invasion (Feng, Feng, & Lv, 2024; Wu, Sun, & Zheng, 2018). Prior to initial enucleation, magnetic resonance imaging (MRI) is increasingly the technique most often utilised in the workup for RB staging and evaluation (Chawla, Chaurasia, et al., 2018). While MRI can be useful in identifying metastatic risk factors, histopathology is a more accurate method for detecting microscopic infiltration (Chawla, Sharma, et al., 2012). The identification of the development pattern, the expansion of the optic nerve involvement, the detection of orbital and/or meningeal extension, and the existence of second tumours are often included in RB evaluation using MRI (Zhu, Zhao, & Zheng, 2025). Furthermore, the ability of surgeons to guarantee a free resection margin may be aided by the identification of optic nerve invasion on MRI in paediatric patients undergoing primary enucleation (De Jong et al., 2015).

Despite the widespread use of MRI in RB staging, there remains a critical research gap regarding the precise diagnostic accuracy of MRI in detecting PLONI. While several individual studies have evaluated MRI's performance, the reported sensitivity and specificity values vary considerably across literature. This variability may stem from differences in imaging protocols, patient populations, radiologist expertise, and diagnostic criteria used across studies. Furthermore, no comprehensive meta-analysis systematically synthesized the available evidence to provide pooled estimates of MRI's diagnostic performance for PLONI detection.

This meta-analysis addresses this gap by consolidating data from multiple studies to establish more reliable estimates of MRI's sensitivity and specificity in identifying PLONI. The novelty of this work lies in its systematic approach to evaluating the diagnostic value of MRI specifically for PLONI, which has direct implications for treatment decision-making. By providing robust pooled estimates, this study offers clinicians evidence-based guidance for incorporating MRI into their diagnostic algorithms, particularly when considering eye-preserving therapies versus enucleation. The purpose of this study is to systematically evaluate the diagnostic performance of MRI in identifying PLONI in retinoblastoma patients through comprehensive meta-analysis of available evidence.

METHOD

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A computerized search was conducted in Google Scholar, PubMed/MEDLINE (U.S. National Library of Medicine), EBSCOhost, and Proquest to identify potentially eligible articles published before September 30, 2023, without language restrictions. The search was expanded by filtering the references listed in the articles. The keywords used to search for articles are "retinoblastoma", "magnetic resonance imaging", “optic nerve invasion”, "sensitivity", "specificity", and "accuracy", with

various variations of word derivatives and combinations of boolean operators according to the protocol of each database.

Studies were included if they met all of the following criteria: (1) The study used MRI to identify optic nerve invasion; (2) studies used histopathology and/or immunohistochemistry results as reference standards; and (3) the study provides sufficient data to assess diagnostic accuracy. The exclusion criteria are as follows: (1) The articles resulting from the search are reviews, guidelines, or editorials; and (2) the data are not detailed enough to evaluate diagnostic performance.

The following data were extracted from the included studies in standard form: study characteristics, namely name of first author, year of publication, country where the study was conducted, study design, sensitivity, and specificity. Assessment of the quality of research methodology was carried out using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) instrument. The QUADAS-2 tool is a validated instrument designed to assess the risk of bias and applicability concerns in diagnostic accuracy studies. It evaluates four key domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed for risk of bias, and the first three domains are also evaluated for applicability concerns. Heterogeneity between studies was assessed with the inconsistency index (I^2): 0–40%, low heterogeneity; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity (Higgins et al., 2011). Two reviewers (M.P., A.A.) independently performed data extraction and quality assessment. Any disagreements between the two reviewers during the data extraction and quality assessment process were resolved through discussion and consensus. In cases where consensus could not be reached, a third reviewer was consulted to make the final decision, ensuring objectivity and accuracy in the data synthesis.

Sensitivity and specificity with corresponding 95% CIs were pooled using random-effects modeling and displayed in forest plots. Publication bias for studies was assessed with the Deeks funnel plot and statistical significance was tested with the Deeks funnel plot asymmetry test. Statistical analysis was performed in the STATA 17.

RESULT AND DISCUSSION

Selection and Data Extraction

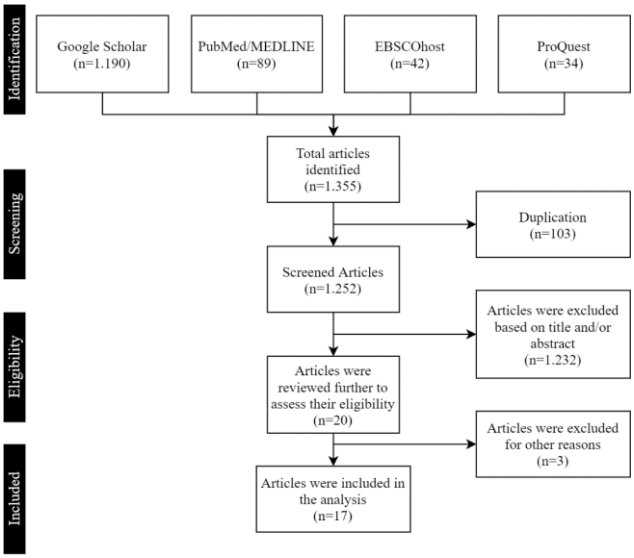

Figure 1. PRISMA Diagram

Based on Figure 1, it can be seen that of the total 1.355 articles identified, there were 17 articles which were then included in the meta-analysis

Quality Assessment

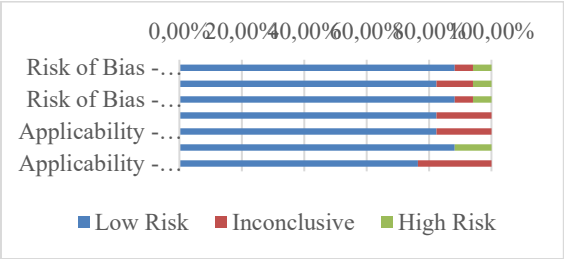

Figure 2. Risk of Bias and Applicability Assessment Using the QUADAS Instrument

Diagnostic Performance

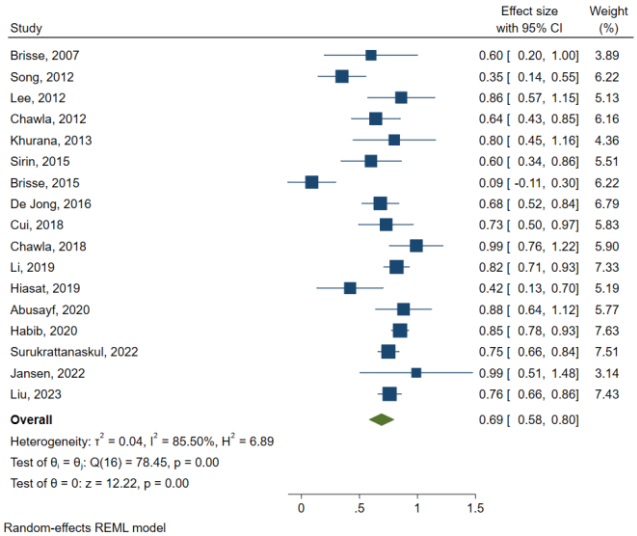

Figure 3. Forest Plot for Sensitivity

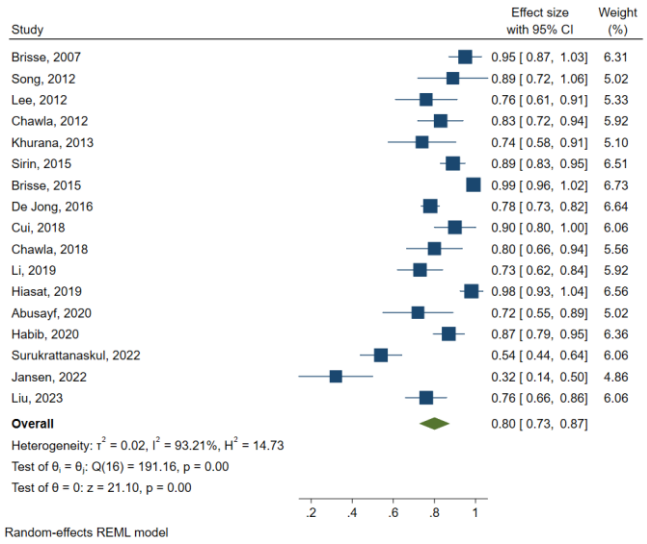

Figure 4. Forest Plot for Specificity

Based on figure 3 and 4, it can be seen that overall sensitivity was 69,0% (95%CI: 58%-80%) and overall specificity was 80,0% (95%CI: 73%-87%). It was also found that heterogeneity was included in the quite large category (I2 = 85,5%).

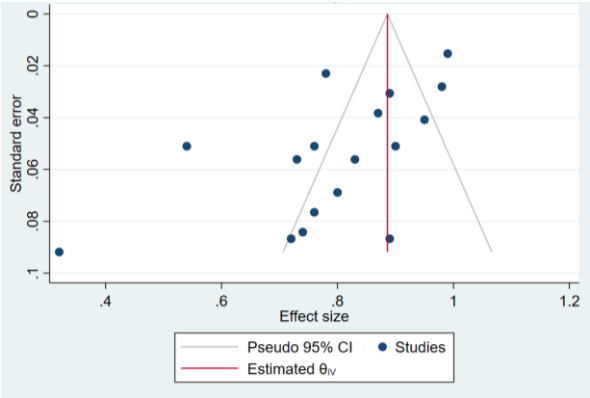

Figure 5. Funnel Plot

Based on Figure 5, it can be seen that the shape of the funnel plot is asymmetrical, so it can be interpreted that the probability of publication bias in this study is low. The high heterogeneity observed in this meta-analysis (I^2 = 85.5%) warrants careful consideration. Several factors may contribute to this substantial variability across studies. First, differences in MRI protocols, including field strength (1.5T vs. 3.0T), sequence parameters, contrast administration protocols, and the use of specialized coils, may influence diagnostic accuracy. Second, variations in patient demographics, such as age distribution, tumor size, and disease stage at presentation, could affect the detectability of PLONI on MRI. Third, differences in radiologist experience and the specific diagnostic criteria used to define PLONI on MRI may introduce inter-observer variability. Fourth, variations in study design, including retrospective versus prospective data collection and differences in reference standard application, may contribute to heterogeneity. Finally, the relatively small sample sizes in some included studies may lead to imprecise estimates that contribute to overall heterogeneity.

Despite this high heterogeneity, the use of a random-effects model in our analysis appropriately accounts for between-study variability, and our assessment using the QUADAS-2 tool and Deeks funnel plot indicates low risk of bias and minimal publication bias. Therefore,

the pooled estimates remain valid and generalizable to clinical practice, though they should be interpreted with recognition of the variability across studies. The invasion of the optic nerve both intra- and prelaminarly is not regarded as a high-risk characteristic. About 8% of patients experience postlaminar optic nerve invasion. Because of the higher risk of metastatic disease and mortality, postlaminar optic nerve invasion usually requires enucleation followed by systemic chemotherapy (Li et al., 2020). The intersection of the optic disc and the midpoint between the enhancing choroid and the low intensity sclera on magnetic resonance imaging can be used to estimate the lamina's location. Histopathology is required for a conclusive diagnosis of postlaminar optic nerve invasion, and it might not be available if eye-preserving therapy is taken into consideration. Tumour extension is typically indicated by thickening and enhancement of the postlaminar optic nerve on magnetic resonance imaging (Silvera et al., 2021).

It can be difficult to correctly categorise more subtle abnormalities at the globe-nerve junction, though. A postlaminar tumour, pre- or intralaminar tumour with a posteriorly displaced lamina cribrosa, central retinal vessels, or inflammation can all be represented by enhancement of the optic nerve at the globe-nerve junction (Brisse et al., 2015). Based on visual evaluation of optic nerve enhancement and tumour size, postlaminar optic nerve invasion can be diagnosed with a sensitivity estimated at 59% and specificity estimated at 94% (Song et al., 2012). Variations in the degree of suspicion, imaging method, and the interpreting radiologist's experience may all contribute to lower accuracy (Hiasat et al., 2019).

Normal optic nerve size, normal optic nerve signal on T2-weighted images, and optic nerve enhancement of ≤ 3 mm on postcontrast imaging are the most dependable direct MR imaging criteria to rule out advanced optic nerve invasion (Brisse et al., 2015). "Double-dot" enhancement, which appears as punctate foci of enhancement straddling the central retinal vessels at the globe-nerve junction, and normal enhancement of the optic nerve's central retinal vessels should not be confused with tumours.38 Furthermore, posterior lamina cribrosa bulging brought on by elevated intraocular pressure may mimic optic nerve invasion and produce a false-positive interpretation. The capacity of MR imaging to identify optic nerve invasion in its early stages is still restricted, and pathology is still the gold standard for identifying high-risk characteristics (Chawla, Chaurasia, et al., 2018).

In the meta-analysis that we conducted on 17 research reports, we found that overall sensitivity was 69,0% (95%CI: 58%-80%) and overall specificity was 80,0% (95%CI: 73%-87%). It was also found that heterogeneity was included in the quite large category (I2 = 85,5%). It is known that a diagnostic tool can be classified to be of good value and high quality if it has a sensitivity and/or specificity of at least 80,0% (Power et al., 2013). Based on this concept, it appears that the specificity of MRI in identifying PLONI is superior to its sensitivity. This finding has important clinical implications for treatment decision-making in retinoblastoma patients. The high specificity (80.0%) indicates that when MRI suggests the presence of PLONI, clinicians can have considerable confidence in this finding, which may guide decisions regarding the need for enucleation versus eye-preserving therapy. Conversely, the moderate sensitivity (69.0%) suggests that MRI may miss approximately one-third of PLONI cases, indicating that a negative MRI result should be interpreted with caution, particularly in high-risk cases. This also shows that the role of MRI to identify PLONI in RB

cases is very important, especially in cases where it has been decided that histopathology should not be performed because eye-preserving therapy is taken into consideration.

In clinical practice, these findings suggest that MRI should be used as part of a comprehensive diagnostic approach rather than as a standalone tool. When MRI indicates PLONI, clinicians can proceed with appropriate aggressive treatment strategies with confidence. However, when MRI is negative for PLONI, especially in patients with other high-risk features, careful clinical judgment and potentially more conservative treatment approaches may be warranted. The integration of MRI findings with clinical examination, tumor characteristics, and other imaging modalities can optimize treatment selection and improve patient outcomes.

The meta-analysis that we have conducted also found high heterogeneity in the summary results. It is important to note that the meta-analysis that we have conducted uses a random effects model and the degree of heterogeneity is identified based on the I2 value. To overcome this, the next appropriate step is to carry out meta-analysis in subgroups, for example based on diagnostic criteria, patient characteristics, sample size, year of publication, keywords used, and so on, as well as carrying out meta-regression. However, both analyzes were not possible for us to carry out due to the limited research reports available to divide into several subgroups. In addition, we have reported a low risk of bias based on the QUADAS instrument and analysis of publication bias (using Deeks funnel plot), so it can be confirmed that the heterogeneity obtained in this study does not affect the validity of the final results of the meta-analysis and the research conclusions can still be generalized in the general population. The meta-analysis that we have conducted has several limitations. First, there were some studies that used a relatively small number of research subjects. Second, this study has high research heterogeneity and variations in analytical techniques cannot be used to reduce it. Third, meta-analysis was not carried out in subgroups and meta-regression was not carried out because the data extraction results showed that both analyzes were not possible to carry out.

Additional limitations of this meta-analysis should be acknowledged. First, variations in MRI protocols across the included studies, such as differences in magnetic field strength, imaging sequences, and contrast administration techniques, may have contributed to heterogeneity and affected the diagnostic accuracy estimates. Second, potential observer bias and inter-rater variability in MRI interpretation were not consistently addressed across all included studies, which may have influenced the reported sensitivity and specificity values. Third, some studies included in this meta-analysis utilized relatively small sample sizes, which may have led to imprecise estimates and contributed to the overall heterogeneity. Fourth, the retrospective design of several included studies may have introduced selection bias and affected the generalizability of findings. Finally, differences in the prevalence of PLONI across study populations may have affected the positive and negative predictive values of MRI in clinical practice.

CONCLUSION

MRI has high specificity in identifying PLONI in RB, so it can be used as a diagnostic modality, especially in cases where eye-preserving therapy is taken into consideration. This is very important because MRI can serve as a valuable tool for evaluating the likelihood of achieving complete tumor removal, estimating the necessary extent of surgical intervention,

and selecting suitable candidates for eye-sparing treatments or neoadjuvant chemotherapy. The findings of this meta-analysis provide evidence-based support for incorporating MRI into the preoperative assessment algorithm for retinoblastoma patients, particularly when weighing the risks and benefits of eye-preserving versus enucleation strategies. Future research should focus on standardizing MRI protocols and developing more refined diagnostic criteria to improve the sensitivity of MRI for PLONI detection while maintaining its high specificity.

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