‘Malignant transformation of hypointense nodules seen only on hepatobiliary phase gadoxetic acid-enhanced MR imaging— A Systematic review and Meta-Analysis’

by

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Abstract

Background: Hypointense nodules detected on the hepatobiliary phase (HBP) of gadoxetic acid–enhanced magnetic resonance imaging (MRI) are frequently seen in patients with chronic liver disease or cirrhosis. Such nodules may represent a spectrum from dysplasia to early hepatocellular carcinoma (HCC), and the development of arterial-phase hyperenhancement and subsequent hypervascular transformation of these lesions is indicative of an increased malignant potential.

Aim: Through a comprehensive systematic review and meta-analysis, this study seeks to evaluate the outcomes of hypointense nodules observed in the hepatobiliary phase on gadoxetic acid-enhanced MRI and to identify the risk factors associated with their hypervascular transformation.

Methods: A computerised search of the Pubmed, Web of Science and Scopus databases was carried out to identify relevant literature reports on hypovascular hypointense nodules in the hepatobiliary phase of gadoxetic acid–enhanced MRI that will eventually undergo hypervascular transformation.

Results: 18 studies were included in this meta-analysis, with 1563 patients and a total of 2136 hypointense hypovascular hepatic nodules. The pooled overall rate of hypervascular transformation was 34.4%, (95% CI: [28.7%, 40.2%]) and $I2$ was 87.4%. The pooled 1-, 2- and 3-year cumulative incidence rates were 19.7% (95% CI: [9.1%, 30.4%]), 27.9%, (95% CI: [16.3%, 39.5%]); and 27.2% (95% CI: [17.7%, 36.7%], respectively. A metaregression analysis revealed that the heterogeneity of malignant transformation was significantly affected by the initial mean nodule size, with a cutoff value of 9 mm.

Conclusion: Hypovascular hypointense nodules observed during the hepatobiliary phase of Gadoxetic acid-enhanced MRI present a considerable risk of progressing to hypervascular hepatocellular carcinomas (HCCs). Initial nodule size is an important predictor of hypervascular transformation, with larger nodules being more likely to undergo this process. This highlights the importance of close monitoring, to enable timely intervention to improve patient outcomes.

Keywords: Hypointense hepatic nodules, Hypovascular nodules, Hepatocellular carcinoma, Hypervascular transformation, Gadoxetic acid, Gd-EOB-DTPA, Magnetic resonance imaging.

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Finally, I would like to dedicate this dissertation to my beloved uncle Robert, who may no longer be with us but who's wisdom and guidance continue to inspire me everyday.

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Abbreviations and Acronyms

AASLD	American Association for the Study of Liver Diseases
ADC	Apparent Diffusion Coefficient
AFP	Alpha-Fetoprotein
CI	Confidence Interval
CLD	Chronic Liver Disease
ctDNA	Circulating Tumour DNA
DCP	Des-γ-Carboxy Prothrombin
DWI	Diffusion-Weighted Imaging
EASL	European Association for the Study of the Liver
Gd-EOB-DTPA	Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid (Gadoxetic Acid)
HBP	Hepatobiliary Phase
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HHN	Hypovascular Hypointense Nodule
MDCT	Multidetector Computed Tomography
MELD	Model for End-Stage Liver Disease
MRI	Magnetic Resonance Imaging

NA	Not Available / Not Applicable
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
OATP	Organic Anion-Transporting Polypeptide
PET	Positron Emission Tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REML	Restricted Maximum Likelihood
TERT	Telomerase Reverse Transcriptase
VEGF	Vascular Endothelial Growth Factor

Chapter 1- Introduction

Advancements in medical imaging, particularly hepatobiliary phase gadoxetic acid-enhanced magnetic resonance imaging (MRI), have significantly enhanced our ability to identify and characterise hepatic lesions. A significant advancement in this field is the detection of hypointense nodules during the hepatobiliary phase, which have a potential for malignant transformation into hepatocellular carcinoma (HCC). The early identification of these high-risk nodules is critical so as to guide patient follow-up and management to ultimately improve patient clinical outcomes.

Gadoxetic acid (also known by the tradenames Primovist ® (Gd-EOB-DTPA) in Europe and Australia, and Eovist ® in the United States) is a hepatocyte-specific MRI contrast agent which has become essential in diagnosing HCC. It is particularly useful for identifying early-stage HCC, as these lesions often demonstrate hypointensity on hepatobiliary-phase imaging. Beyond diagnosis, gadoxetic acid may also provide functional information that aids in the characterisation of focal liver lesions, assessing therapeutic responses, and evaluating liver fibrosis (Y.Y. Kim et al., 2019).

Dynamic imaging using gadoxetic acid-enhanced MRI often reveals hypointense lesions in the hepatobiliary phase, even when these lesions do not exhibit hypervascularity. Such lesions are significant due to their potential for malignant transformation through multistep hepatocarcinogenesis. The transformation process is complex and is influenced by changes in the hepatic tissues and vascular architecture. During this process, a decrease in the expression of organic anion-transporting polypeptide 8 (OATP8), which is a crucial uptake transporter for gadoxetic acid in hepatocytes, is observed. This decrease in OATP8 expression

occurs at an earlier stage of hepatocarcinogenesis compared to the vascular changes seen in advanced HCC.

Both HCC and premalignant cirrhosis-associated hepatic nodules can present as hypointense lesions without arterial phase enhancement on gadoxetic acid-enhanced MRI (Joo et al., 2016). Therefore, close monitoring of these lesions is essential for effective management. Understanding the clinical implications and potential outcomes of hypovascular nodules allows for appropriate treatment interventions and may improve patient prognosis. Moreover, understanding the transformation pathways aids in developing better-targeted therapies aimed at halting or reversing the progression of these nodules.

The factors that predict the hypervascular transformation of hypovascular nodules have been the subject of various studies. The primary risk factors identified include the **initial size and growth rate** of the nodule, as larger nodules or those that grow quickly are more likely to undergo malignant transformation; **specific imaging features**, such as hypointensity during the hepatobiliary phase and hyperintensity on T2-weighted imaging, which indicate a higher potential for transformation; and **patient cohorts** with a history of chronic liver disease, cirrhosis, or prior HCC (Teerasamit et al., 2023).

The aim of this meta-analysis is to provide a thorough assessment of the hypervascular transformation of hypointense hypovascular nodules during the hepatobiliary phase of gadoxetic acid-enhanced MRI, along with the related risk factors. Despite the increasing use of MRI in clinical practice, there remains limited consensus on the incidence rates of lesion progression over time and the respective risk factors that predispose these nodules to undergo malignant transformation. In light of this, this meta-analysis integrates the existing data with particular focus on quantifying the overall incidence rate of hypervascular transformation as well as the

rate of transformation at various follow-up points, namely at 1, 2, and 3 years, and evaluating the influence of various clinical and radiological characteristics on this process.

The research methodology involves a systematic search strategy across multiple electronic databases, including PubMed, Web of Science, and Scopus, to ensure a comprehensive extraction of the relevant literature. To enhance the reproducibility and transparency of the review process, the study follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and a PRISMA flow diagram was used to visually depict each stage of the article screening and selection process. To make sure that only relevant, high-quality studies are included in the analysis, inclusion and exclusion criteria were then applied.

The basis of the study's analytical approach lies in pooling the reported incidence rates of each of the studies included in this meta-analysis into an overall estimate for each follow-up interval. Using advanced statistical models such as the DerSimonian-Laird random-effects meta-analysis, the review analyses the proportion of hypointense nodules that progress to hypervascular nodules over 1-, 2-, and 3-year periods, providing precise pooled estimates along with 95% confidence intervals. These findings shed light on the temporal dynamics of lesion progression and offer critical information for clinicians in stratifying patients according to their risk profiles. To further assess the heterogeneity observed across studies, the analysis incorporates meta-regression techniques exploring covariates such as initial nodule size, patient age, underlying etiology of liver disease, and technical variables such as MRI scanner strength. This exploration aims to identify key predictors of transformation, aiding surveillance and treatment planning.

This meta-analysis ultimately underscores the need for clinicians to integrate imaging findings with clinical and laboratory data to make informed decisions

regarding intervention timing. As knowledge in this field develops further, existing guidelines on the follow-up of hypovascular hypointense nodules on MRI can become increasingly patient-centric with surveillance protocols aimed at early detection of malignant transformation, thereby reducing the burden of advanced HCC and improving prognosis for high-risk patient populations.

Chapter 2 - Literature Review

Hepatocellular carcinoma (HCC) continues to be a significant global health concern and a primary contributor to cancer-related mortality, especially in regions with a high incidence of chronic viral hepatitis and increasing rates of metabolic liver disease (El-Serag & Marrero, 2020). HCC develops through a sequential pathogenic cascade in which persistent hepatic injury triggers repeated cycles of cellular necrosis, regeneration, and accumulating genomic alterations (Campani et al., 2023). In recent years, advancements in imaging technology have significantly enhanced our understanding of early hepatocarcinogenesis, thereby increasing the likelihood of early detection and curative treatment. Gadoxetic acid–enhanced MRI has become a key imaging advancement, primarily because its hepatocyte-specific hepatobiliary phase (HBP) imaging reveals how hepatocytes function and how organic anion-transporting polypeptides (OATPs) are expressed.

Within this diagnostic framework, hypovascular hypointense nodules (HHNs), which are defined as lesions that do not enhance on arterial-phase imaging and are hypointense on the HBP, pose both a diagnostic challenge and a clinical dilemma. HHNs encompass a histopathologic spectrum that includes regenerative nodules, low- and high-grade dysplastic nodules, and early HCC that has not yet acquired angiogenic neo-vascularisation. The clinical significance of HHNs lies in their potential to transform into hypervascular HCC over variable time frames. Consequently, identifying which nodules will advance to HCC is a key factor with significant consequences for surveillance, biopsy, intervention, and transplant eligibility. This review summarises the current literature on the natural history of HHNs, examines imaging and clinical risk factors predictive of malignant

transformation, discusses management approaches informed by existing evidence, and outlines areas for future study.

2.1 Definition and pathophysiology

Hypovascular hypointense nodules are identified on multiphasic gadoxetic acid–enhanced MRI as focal lesions that lack definite arterial-phase hyperenhancement and demonstrate decreased signal intensity relative to surrounding liver parenchyma on the HBP (normally performed 15–20 minutes post-injection) (Ozaki et al., 2025). The HBP signal is dependent on the uptake of gadoxetic acid into hepatocytes via OATPs (particularly OATP1B3); the loss of transporter expression during hepatocarcinogenesis results in a diminished HBP signal and, therefore, HBP hypointensity in dysplastic or malignant lesions (Motosugi et al., 2011). The absence of arterial hyperenhancement at initial detection does not rule out malignant potential, because early HCC can be iso- or hypovascular before the angiogenic switch, inferring hypervascular transformation (International Working Group on Hepatocellular Neoplasia, 2010). Pathologically, early-stage malignant nodules can be well-differentiated and microscopically invasive but lack the blood supply characteristic of progressed HCC, accounting for this imaging phenotype.

2.2 Epidemiology and observed transformation rates

Multiple retrospective studies and single-centre series have documented the frequency and outcomes of HHNs in populations with chronic liver disease. Depending on the study design, inclusion criteria, and observation intervals, transformation rates reported in the literature vary widely, ranging from low single-digit percentages in some cohorts to over two-thirds in others (Hyodo et al., 2013; Saitoh et al., 2018; Teerasamit et al., 2023). Many large studies illustrate this heterogeneity and highlight the factors that affect the transformation risk.

Teerasamit et al. (2023) examined HHNs in a cohort of patients with chronic liver disease and reported a transformation rate of approximately 45% over a mean follow-up of 674 days. Their study included patients with various aetiologies and highlighted that nearly half of the nodules developed imaging features consistent with HCC within a relatively short follow-up period. On the other hand, Saitoh et al. (2018) reported a lower transformation rate of 16.5% over a longer median follow-up of approximately 1,173 days, suggesting that patient selection and baseline risk have a significant influence on the cumulative incidence rate. Earlier literature and smaller series have described transformation rates ranging from approximately 8.5% to over 50%. Heterogeneity in lesion selection, imaging methods, and outcome definitions complicates meta-analytic synthesis.

The reasons for variability across published studies include the following:

- **Differences in baseline patient risk:** The transformation rates of cohorts enriched for viral hepatitis, cirrhosis, or prior HCC are typically higher than those of unselected or non-cirrhotic populations.

- **Variation in imaging technique and definitions:** the definition of “hypovascular” varies across studies. Some studies define ‘hypovascular’ as a strict absence of arterial enhancement, while others include equivocal or faint enhancement. HBP imaging timing and MRI field strength also differ.

- **Surveillance intensity and follow-up duration:** studies with more frequent imaging or longer follow-up are more likely to detect transformation events, whereas studies carried out over a shorter timeframe may underestimate long-term risk.

- **Endpoint ascertainment:** a subset of studies defines progression purely by the presence of arterial hyperenhancement, while others require growth criteria, additional imaging hallmarks, or histopathologic confirmation.

Overall, the research supports the conclusion that HHNs have a non-negligible risk of developing overt HCC, and that both patient clinical characteristics and lesion-specific imaging features influence this risk.

2.3 Temporal aspects and kinetics of transformation

HHNs have variable temporal behaviours. Some nodules undergo rapid conversion to hypervascular HCC within several months, while others remain indolent for years or may even regress.

Studies that observed hypervascular transformation have reported varying median times to transformation. The majority of studies report median times in the range of 6-24 months, with the majority undergoing hypervascular transformation within the first 12 months. In cohorts where the median time to arterial hypervascularisation was short, aggressive surveillance allowed early detection and timely intervention (Yoon et al., 2012; Teerasamit et al., 2023). However, other cohorts report longer median times. This variability illustrates biological heterogeneity, whereby some nodules are already genomically advanced but angiogenically silent, while others may require cumulative genetic hits and microenvironmental changes before conversion.

This temporal heterogeneity guides surveillance strategies. Nodules with higher-risk features benefit from short-interval imaging (e.g., 3 months), while longer-interval

follow-up would be sufficient for small lesions with no features of overt concern. Furthermore, the observation that many transformations occur within the first two years suggests that increased vigilance during this period improves early detection, although sustained longer-term surveillance also remains important, given the delayed conversions in a minority of nodules.

2.4 Imaging features indicative of malignant transformation.

Imaging is the primary non-invasive technique for risk stratification of HHN, and several imaging characteristics have been shown to have prognostic significance. The following are the primary imaging characteristics highlighted in published studies.

2.4.1 Lesion size

Nodule size at baseline is one of the most reproducible predictors of progression. Generally, nodules ≥10 mm (and especially ≥15 mm) show greater rates of transformation to arterial-enhancing HCC than subcentimeter lesions (Saitoh et al., 2018). Studies differ in their size thresholds, but an operational method frequently employed in clinical practice separates nodules smaller than 10 mm (lower risk) from those 10 mm or larger (higher risk) when determining surveillance intervals and considering biopsy.

2.4.2 Diffusion-weighted imaging (DWI) and ADC mapping

Restricted diffusion on MRI, as demonstrated by high signal on high b-value DWI (b1000) and a correspondingly low apparent diffusion coefficient (ADC), is associated with higher cellular density and is predictive of malignant potential. Research indicates that HHNs demonstrating diffusion restriction have a higher

likelihood of advancing to HCC, and ADC values may function as a continuous biomarker for transformation risk (Koh et al., 2015). Quantitative ADC thresholds vary, and overlap between benign and malignant entities limits specificity, but DWI adds predictive value when combined with other MRI features.

2.4.3 T2-weighted signal intensity

Hyperintensity on T2-weighted sequences can be a marker of increased water content and architectural disruption. Nodules with mild to moderate T2 hyperintensity are more often dysplastic or malignant when compared to T2-hypointense lesions. However, T2 signal is less specific than DWI and should be interpreted in the context of other imaging and clinical features.

2.4.4 Degree and pattern of hepatobiliary-phase hypointensity.

The extent of HBP hypointensity relative to liver parenchyma is an essential factor. Significant and well-demarcated hypointensity, as well as heterogeneous internal signal, have been associated with higher malignant conversion rates compared to mild or equivocal hypointensity (Ozaki et al., 2025). Patterns such as nodule-in-nodule architecture, where a smaller internal nodule exhibits different imaging characteristics from the surrounding lesion, suggest focal dedifferentiation and an increased risk.

2.4.5 Additional dynamic features: corona enhancement, perinodular changes, and late enhancement patterns.

There are a few dynamic features observed during the late arterial to early portal venous phases that correlate with malignant potential. Corona enhancement is a feature that is defined as transient perinodular enhancement, which is thought to reflect abnormal venous drainage and perinodular hyperaemia and correlates with

early HCC and tumour invasiveness. Similarly, intralesional fat content and evidence of internal heterogeneity on dynamic sequences may indicate dedifferentiation. Although they are not conclusive on their own, these ancillary characteristics help create a complete risk assessment.

2.5 Radiomics and quantitative imaging

Quantitative metrics, such as lesion-to-liver contrast ratios for HBP, ADC values, and enhancement kinetics, provide numeric variables for modelling. Radiomics extracts hundreds to thousands of imaging features (texture, shape, and intensity distributions) that machine learning algorithms can integrate with clinical data to produce predictive models. Initial research indicates that radiomics-based classifiers may surpass traditional single-parameter risk stratification; however, generalisability, reproducibility across scanners and protocols, and prospective validation are essential subsequent measures (Liu et al., 2020).

2.6 Clinical Risk Factors

Clinical risk factors pertaining to the patient modify the risk of potential malignant transformation of any given HHN.

Underlying liver disease severity and the presence of cirrhosis are significant risk factors. Cirrhosis is a major driver of hepatocarcinogenesis and has consistently been associated with increased risk of HHN progression. Cirrhotic tissue creates a pro-oncogenic microenvironment, characterised by sustained inflammation, fibrosis, regenerative nodules, and altered vascular architecture, all of which facilitate clonal evolution. Measures of portal hypertension and synthetic dysfunction (e.g., Child-Pugh class) also have an impact on management decisions, particularly regarding the suitability of biopsy or surgical intervention.

2.6.1 Aetiology of liver disease

Aetiological factors influence the baseline risk of hepatocellular carcinoma and potentially the natural history of hypovascular hypointense nodules. Chronic hepatitis B virus (HBV) infection can induce carcinogenesis through the direct oncogenic effects of viral integration and mutated host genes, even in noncirrhotic livers, potentially leading to different patterns of lesion behaviour compared with hepatitis C (HCV)- or NAFLD-related diseases (Chen et al., 2006). The effect of modern antiviral treatments, such as nucleotide analogues for HBV and direct-acting antivirals for HCV, on the risk of individual nodule transformation is not yet fully understood. However, viral suppression has been shown to decrease the overall incidence of HCC and may slow the progression of lesions at the population level.

A prior history of HCC predicts higher transformation rates among HHNs, likely reflecting a field effect and underlying genomic instability in the cirrhotic liver that predisposes to multifocal tumorigenesis. Many cohorts enriched for patients with prior HCC report higher cumulative transformation probabilities, reinforcing the need for intense surveillance in this subgroup (Sasaki et al., 2016).

2.6.2 Serum biomarkers

Serum tumour markers such as alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) provide additional information but lack sufficient sensitivity for early HCC. Rising or newly elevated biomarkers in association with imaging changes raise suspicion for malignant transformation. However, stable or normal biomarkers do not exclude progression. Combining imaging-derived variables with serum biomarkers may enhance the ability to predict which HHNs have the potential to undergo malignant transformation (Llovet et al., 2018).

2.6.3 Risk stratification frameworks and predictive modeling

Due to the numerous imaging and clinical predictors, various groups have created composite risk scores or predictive nomograms to assess the likelihood of HHN progression. Typical components include lesion size, DWI characteristics, HBP contrast-to-liver ratio, presence of T2 hyperintensity, cirrhosis, and a history of prior HCC. Such integrated models generally outperform single-feature assessments, enabling more individualised surveillance strategies. Nevertheless, diversity in model construction, differences in imaging acquisition parameters, and limited external validation impede broad clinical application. To incorporate these models into guidelines, imaging protocols must be standardised and prospectively validated across multiple institutions (Teerasamit et al., 2023).

2.6.4 Pathological and molecular correlates of progression

Histopathological examinations of HHNs that subsequently undergo transformation typically exhibit characteristics indicative of high-grade dysplasia or early well-differentiated HCC. Molecular analyses indicate that the acquisition of driver alterations, such as telomerase reverse transcriptase (TERT) promoter mutations, TP53 perturbations, and the activation or suppression of signalling pathways (Wnt/β-catenin, PI3K/AKT), is a progressive and cumulative process during hepatocarcinogenesis (Zucman-Rossi et al., 2015). HBP hypointensity is caused by a loss of hepatocellular activity in the form of decreased OATP expression, particularly OATP1B3. On the other hand, the arterial hypervascular phenotype, which forms the basis for standard non-invasive HCC diagnostic criteria, is produced by the angiogenic switch, mediated by VEGF and other pro-angiogenic factors. The molecular heterogeneity of HHNs is significant because it implies that while some

lesions may never achieve the complete set of changes required for invasive cancer, others may be genetically primed for rapid malignant conversion.

2.7 Management strategies: Surveillance, Biopsy, and Intervention

The detection of an HHN prompts clinical decision-making that balances the risks of missed early HCC against the harms of unnecessary invasive procedures.

2.7.1 Surveillance strategies

A risk-adapted surveillance strategy is practical and grounded in data.

Low-risk HHNs presenting with the following features: small (<10 mm), absent DWI restriction, minimal HBP hypointensity, no history of HCC, and preserved hepatic function, merit a repeat gadoxetic acid MRI at 3–6 months to assess interval change. If stable, the imaging interval can be extended to 6–12 months, maintaining standard HCC surveillance per guidelines.

Intermediate-risk HHNs measuring 10–15 mm in size, with equivocal ancillary features or modestly abnormal biomarkers, merit repeat MRI at 3 months and closer follow-up. Multidisciplinary review is also appropriate in these cases.

High-risk HHNs include nodules measuring more than 10–15 mm or those with DWI restriction, marked HBP hypointensity, corona enhancement, prior HCC, cirrhosis, or rising serum biomarkers. Follow-up considerations for these nodules include early repeat imaging within 3 months, consideration of targeted percutaneous biopsy if the results will change management, and discussion regarding locoregional therapy when conversion is observed.

These pragmatic recommendations reflect standard practice in many centres, but they are primarily based on retrospective evidence. The frequency and duration of surveillance should be individualised and discussed in multidisciplinary settings.

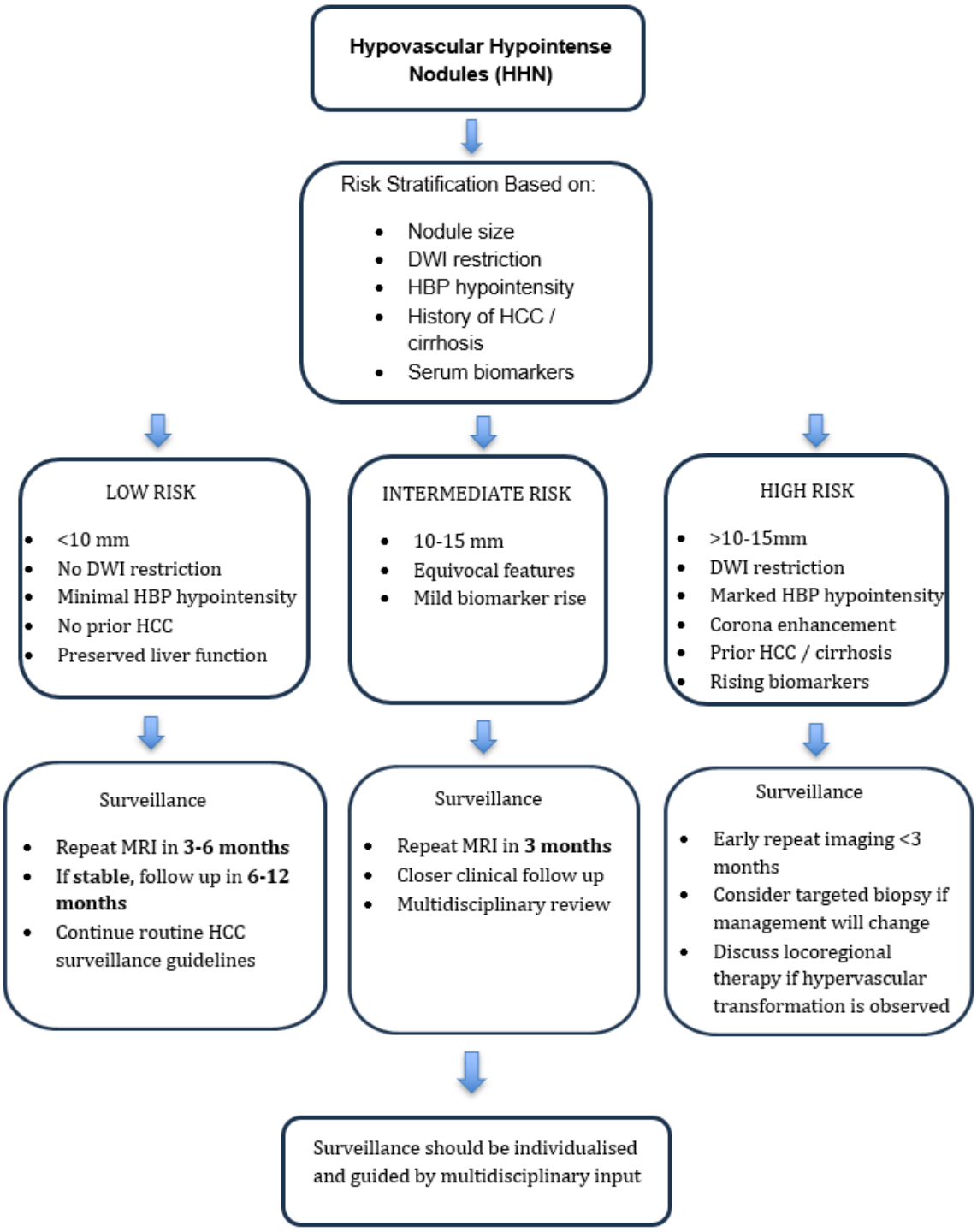

Figure 1: Flowchart highlighting surveillance strategies of Hypovascular Hypointense Nodules

2.7.2 Role and limitations of biopsy

Although biopsies have limitations in early small HHNs, they can provide histological confirmation and possible molecular information. False negative results can result from sampling errors, and cirrhotic patients should be aware of procedural risks (such as bleeding and tumour seeding). The greatest indication for biopsy is when histologic confirmation will alter management (e.g., eligibility for transplantation or when considering systemic therapy) or when imaging and clinical assessments are discordant. If clinical suspicion is still present, a negative biopsy does not negate the need for ongoing, thorough imaging follow-up.

2.7.3 Watchful waiting versus early intervention

Therapeutic interventions, including surgical resection, thermal ablation, or transplantation, are typically reserved for lesions that meet established non-invasive imaging criteria for HCC or those that are histologically proven. When there is strong evidence of progression or a significant risk of waitlist dropout, some centres might consider early local therapy for a subset of high-risk HHNs in patients with favourable surgical risk or transplant candidates. Due to a lack of comparative effectiveness data, multidisciplinary teams should make individual decisions regarding the outcomes of preemptive treatment versus surveillance for HHNs. For small, early HCC detected after hypervascular conversion, ablation provides a minimally invasive, curative option that has been shown to be effective. The most imperative factor is early detection, which keeps lesions within manageable size ranges.

In transplant candidates, HHNs complicate staging and allocation decisions. A nodule that transforms to convincing HCC may confer Model for End-Stage Liver Disease (MELD) exception points or other priority adjustments, whereas

indeterminate nodules necessitate careful documentation and often intensified surveillance. Some transplant centres have protocols for preemptive locoregional treatment of suspicious nodules to prevent progression while awaiting transplantation; practices vary and should be guided by local policies, multidisciplinary consensus, and evidence-informed risk-benefit assessments.

Standardised MRI acquisition techniques and reporting templates are necessary for reliable longitudinal evaluation. Key elements include consistent HBP timing, use of DWI with multiple b-values and ADC mapping, clear documentation of lesion size, morphology, T2 and DWI characteristics, degree of HBP hypointensity (qualitative or semi-quantitative), presence of ancillary dynamic features, and comparison with prior studies. Using standardised radiology reports, such as LI-RADS-style descriptors for ambiguous nodules, facilitates communication among hepatology, radiology, and surgical teams, enabling them to make informed decisions. Combining image registries with centralised lesion tracking systems makes it easier to follow surveillance intervals and speeds up multidisciplinary assessments.

2.8 Limitations of current evidence and methodological considerations

The majority of published research on HHNs is retrospective, single-centre and susceptible to selection bias. The variability of imaging methods, definitions, and endpoints compromises the generalisability of the results. There are a limited number of prospective multicenter cohorts utilising standardised MRI techniques and predefined transformation objectives. Additionally, randomised trials assessing varying surveillance intensities or early intervention strategies are lacking. These restrictions hinder the formulation of high-quality guideline suggestions and require caution in the adoption of standardised management frameworks.

Innovative technologies and prospective pathways offer considerable potential for enhancing the risk assessment and management of high-risk HHNs. Radiomics, which involves the extensive extraction of quantitative imaging characteristics and the use of machine learning techniques, has shown promise in improving the accuracy of predicting HHN progression compared to traditional imaging descriptors. Combining radiomic data with clinical variables—such as liver function, previous history of HCC, and pertinent biomarkers—alongside genomic information, may facilitate the creation of robust, personalised risk models. Standardising feature extraction across various imaging platforms, compiling large-scale training datasets, conducting external validation studies, and creating prospective clinical trials to assess their impact on patient outcomes and workflow efficiency are essential steps in achieving this potential (Liu et al., 2020).

In addition to imaging advancements, molecular biomarkers and liquid biopsy techniques are emerging as promising tools for early detection of neoplastic transformation. Circulating tumour DNA (ctDNA), tumour-specific methylation patterns, circulating microRNAs, and other liquid biopsy approaches may enable detection of early malignant changes well before significant vascular remodelling becomes apparent on imaging (Tang et al., 2016). Combining these molecular signals with imaging-based risk stratification could enable earlier intervention, potentially improving prognosis. To this end, systematic prospective studies are necessary to determine the sensitivity, specificity, temporal dynamics, and practical thresholds for clinical implementation. Parallel advances in molecular characterisation, such as the development of novel PET tracers targeting proliferation, angiogenesis, or amino acid transport, offer additional functional insights. Hybrid PET/MRI imaging further enhances this approach by providing simultaneous metabolic and high-resolution multiparametric imaging (Y.Y. Kim et al.,

2019). These innovations aim to refine lesion characterisation, identify specific molecular targets, and guide targeted prevention strategies, such as modulation of proinflammatory, proangiogenic, or oncogenic pathways in high-risk nodules. Concurrently, health services research focused on evaluating the cost-effectiveness, health system implications, and optimal integration of these advanced technologies, such as radiomics-guided triage and centralised lesion tracking, is critical (Liu et al., 2020). The implementation of such initiatives will facilitate the integration of new diagnostics into routine clinical care, ensure equitable access, and inform evidence-based policy decisions. Additionally, it will optimise patient outcomes and reduce the need for unnecessary procedures.

In summary, risk-adapted surveillance that balances the risks of unnecessary interventions against the early detection of curable disease is necessary in clinical practice today for HHNs. This surveillance should utilise multiparametric MRI features and clinical context. Standardisation of imaging protocols, structured reporting, multidisciplinary care, and continued research collaboration are essential to optimising outcomes for patients with HHNs and reducing the substantial burden of HCC worldwide.

Chapter 3 – Method

A systematic search for relevant studies was conducted across multiple electronic databases to ensure comprehensive coverage of the available literature reports on hypovascular hypointense nodules in the hepatobiliary phase of gadoxetic acid–enhanced MRI, which are likely to undergo hypervascular transformation. The databases searched were PubMed, Web of Science and Scopus.

The search string used was as follows: (“HCC” OR “hepatocellular carcinoma” OR “hepato-cellular carcinoma” OR “neoplasm” OR “neoplastic transformation” OR “high grade dysplasia” OR “malignant transformation” OR “arterial phase enhancement”) AND (“without arterial phase hyperenhancement” OR “hypovascular” OR “hypointense” OR “low signal intensity” OR “non-hypervascular”) AND (“nodule” OR “lesion” OR “mass”) AND (“gadoxetic acid–enhanced” OR “Gd-EOB-DTPA” OR “Gd-EOB” OR “gadoxetic acid” OR “gadoxetic” OR “gadoxetate disodium” OR “Primovist” OR “Eovist” OR “Gadolinium” OR “hepatocyte phase” OR “hepatobiliary phase” OR “contrast”) AND (“hepatic” OR “liver”) AND (“MRI” OR “magnetic resonance”). The first search date was established as January 2012, and the literature search was updated till December 2024. To include all relevant articles, references of included articles and pertinent reviews were screened manually. Citation tracking was also performed to minimise publication bias. All search strategies were documented to ensure reproducibility.

The results from this computerised search were imported into ‘Rayyan.ai’, a systematic review management software. This allowed for de-duplication and organisation of the initial records identified.

3.1 QUADAS – 2 Tool (Quality Assessment of Diagnostic Accuracy Studies-2)

To assess the internal validity (risk of bias) and external validity (applicability) of evidence derived from diagnostic test accuracy studies, the QUADAS-2 tool was employed. This tool evaluates studies based on four primary domains: patient selection, index test, reference standard, and flow and timing. The distribution of judgements is summarised in figures 2 and 3 below.

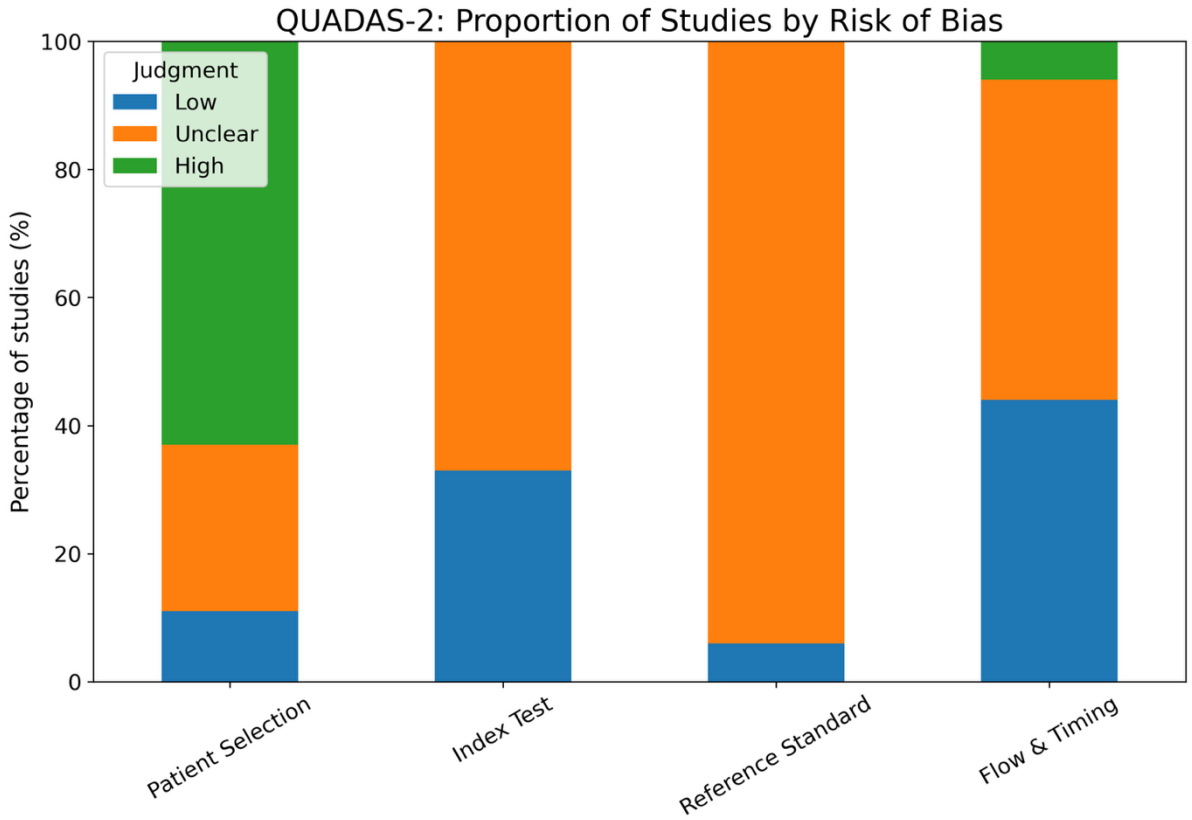

Figure 2 : QUADAS-2 assessment of risk of bias across included studies. Stacked bar chart illustrating the proportion of studies judged as having low, unclear, or high risk of bias in each QUADAS-2 domain.

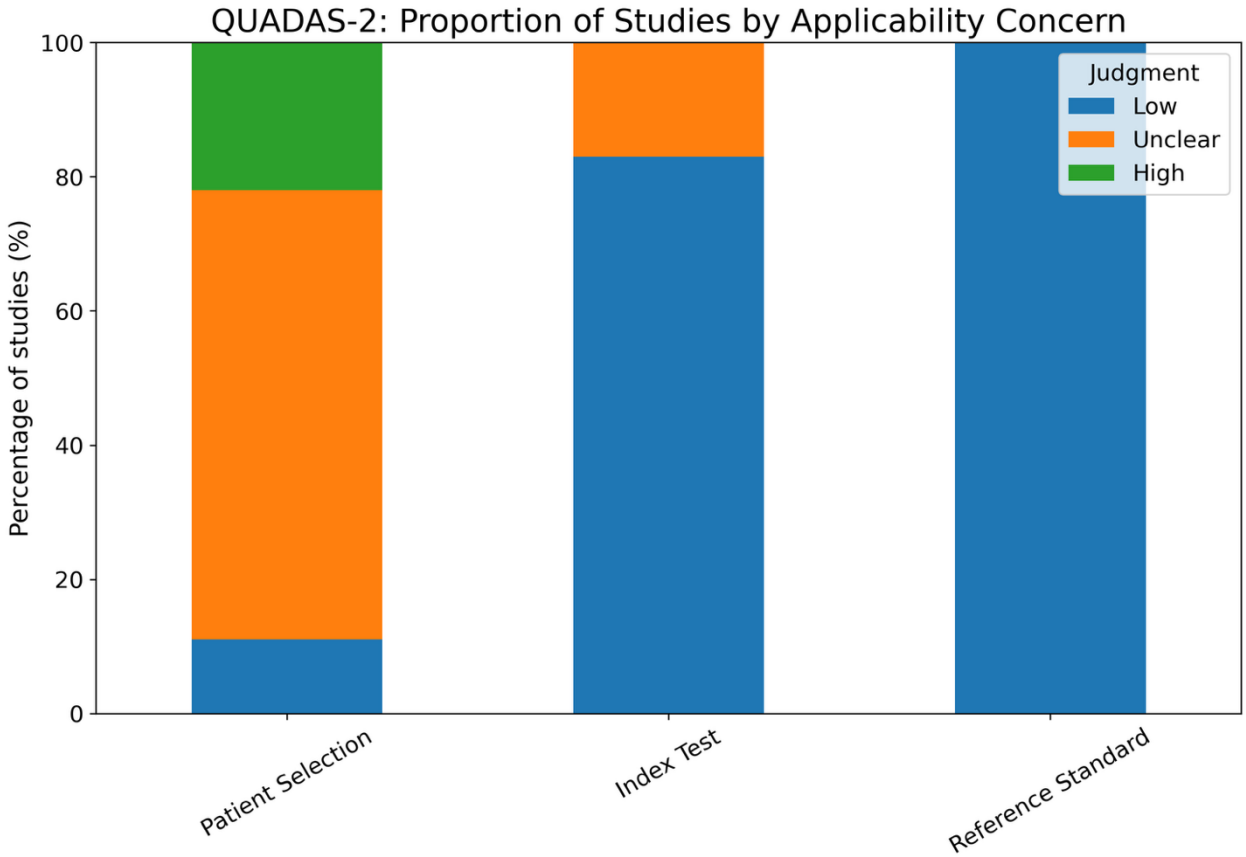

Figure 3: QUADAS-2 assessment of applicability concerns across included studies. Stacked bar chart illustrating the proportion of studies with low, unclear, or high applicability concerns for patient selection, index test, and reference standard.

Overall, the studies exhibited a moderate level of bias risk. The patient selection domain exhibited the most significant concern, with some studies classified as high or ambiguous risk owing to retrospective design, non-consecutive enrolment, or inadequate reporting of inclusion criteria. The index test domain was generally assessed as presenting an unclear risk, primarily due to the inconsistent reporting of blinding during MRI interpretation with respect to follow-up outcomes. For the reference standard, numerous studies depended on imaging follow-up rather than histopathology to verify malignant transformation, leading to an ambiguous risk of bias, although this method aligns with standard clinical practice. Most studies demonstrated a low risk of bias regarding flow and timing, reflecting suitable follow-up and proper consideration of the included nodules.

Concerns related to applicability were generally minimal across all domains. The patient populations, imaging modalities, and outcome criteria employed in the included studies were closely aligned with the objectives of this review, thereby reinforcing the significance of the aggregated findings.

In summary, although certain methodological limitations were noted, particularly concerning patient selection and outcome verification, the overall relevance of the evidence was high, and the studies were deemed appropriate for inclusion in the meta-analysis.

3.2 Inclusion Criteria

Primary research studies, or subsets of larger studies, that specifically examined both the outcomes and potential risk factors related to the hypervascular transformation of hypovascular, hypointense hepatic nodules identified on gadoxetic acid–enhanced MRI were included. To guarantee uniformity and comparability among the included reports, each study was required to meet all of the following established criteria:

3.2.1 Criteria for imaging and study population

The study cohort was required to consist of more than ten patients diagnosed with chronic liver disease (including as alcoholic liver disease, chronic hepatitis C, chronic hepatitis B, and non-alcoholic fatty liver disease) and cirrhosis, who underwent gadoxetic acid-enhanced MRI as part of their clinical evaluation and revealed hypovascular, hypointense nodules.

For the purpose of this review, hypovascular, hypointense nodules were defined as focal hepatic lesions exhibiting diminished or absent arterial-phase enhancement (hypovascularity) and reduced signal intensity (hypointensity) during the hepatobiliary phase of gadoxetic acid–enhanced MRI. This dual imaging criterion was employed to ascertain that the nodules included represented a consistent lesion phenotype across trials.

3.2.2 Reference standard for the final diagnosis

Studies required the use of validated reference standards to establish final diagnoses for the nodules of interest. Acceptable reference standards included histopathologic confirmation from surgical resection or biopsy specimens and/or

characteristic imaging evolution documented on serial follow-up imaging with multidetector computed tomography (MDCT) or MRI. When histopathology was not available for every lesion, well-documented imaging criteria on serial follow-up were accepted as an alternative reference, provided that these criteria were clearly described and consistent with established imaging definitions for hypervascular hepatocellular carcinoma (HCC). Studies relying solely on unverified or poorly described diagnostic approaches were excluded.

3.2.3 Study Design

Eligible studies employed an observational design. Both retrospective and prospective cohort studies were eligible, as these methodologies are appropriate for assessing the incidence of lesions detected on imaging and their progression over time, as well as for investigating related risk factors. Interventional trials were not required but could be considered if they provided pertinent observational outcome data for the nodules of interest without adding treatment-related selection bias.

3.2.4 Outcomes and data reporting

For the quantitative synthesis and meta-analysis of incidence rates, studies needed to provide outcome data with sufficient clarity to enable the calculation of overall or cumulative incidence rates of hypervascular transformation in hypovascular, hypointense nodules. This included the documentation of the initial number of nodules, the quantity (or percentage) of nodules that underwent hypervascular transformation throughout the follow-up period, and the duration until transformation or a sufficient follow-up period to allow estimation of cumulative incidence. Studies that included subgroup analyses, such as by nodule size, baseline imaging characteristics, or underlying liver disease aetiology, were accepted if the primary outcome data were still accessible.

3.3 Exclusion Criteria

To maintain the methodological integrity of the review and to mitigate bias, the following categories of articles and data sources were eliminated.

3.3.1 Small case reports and case series

Case reports and case series with fewer than ten patients were omitted due to their susceptibility to selection bias and inability to yield reliable incidence estimates. Review articles, systematic reviews, editorials, narrative commentary, letters to the editor, and conference abstracts or proceedings were also excluded, as they do not provide original patient-level data that can be used for pooled analysis.

3.3.2 Studies with potential selection bias

Studies demonstrating indications of non-consecutive patient inclusion, ambiguous or selective recruitment methodologies, or other sources of selection bias were omitted.

3.3.3 Studies that are not related to the topic

Studies that did not investigate the outcomes of hypovascular hypointense nodules identified in the hepatobiliary phase of gadoxetic acid-enhanced MRI were excluded, specifically those studies concentrating solely on hypervascular lesions, purely technical imaging comparisons without lesion outcome data, or unrelated hepatic pathology.

3.3.4 Insufficient data for outcome assessment

Studies that did not provide adequate quantitative data for calculating overall or cumulative incidence rates, for instance, those offering purely qualitative descriptions of lesion behaviour without numerical counts or follow-up lengths, were omitted.

3.4.5 Overlapping groups of patients

When multiple reports appeared to include overlapping patient cohorts, such as publications from the same institution covering similar time periods, redundant datasets were excluded to prevent double-counting. In such cases, the most comprehensive or most recent report that provided the greatest detail required for analysis was included.

Table 1: Summary of Inclusion and Exclusion Criteria

Category	**Criteria**
Inclusion Criteria	
Imaging & Study Population	• >10 patients with chronic liver disease (HBV, HCV, alcoholic liver disease, NAFLD) and cirrhosis. • Underwent gadoxetic acid–enhanced MRI. • Presence of hypovascular, hypointense hepatic nodules, defined as: o **Hypovascular**: diminished or absent arterial-phase enhancement. o **Hypointense**: reduced signal intensity on hepatobiliary phase.

Reference Standard for Final Diagnosis	• Histopathology from resection or biopsy and/or imaging evolution on serial MDCT or MRI. • Imaging follow-up must use clearly defined criteria consistent with established definitions for hypervascular HCC.
Study Design	• Observational cohort studies (retrospective or prospective).
Outcomes and Data Reporting	• Provide enough data to calculate the incidence of hypervascular transformation: o Number of baseline nodules. o Number/percentage undergoing hypervascular transformation. o Time to transformation or adequate follow-up duration. • Subgroup data (e.g., nodule size, baseline imaging features, liver disease aetiology) acceptable if the primary outcome remains extractable.
Exclusion Criteria	
Small Case Reports/Case Series	• Case reports or series with <10 patients. • Review articles, systematic reviews, editorials, commentaries, letters, conference abstracts.

Studies with Selection Bias	▪ Non-consecutive enrolment. ▪ Ambiguous or selective recruitment. • Other evidence of biased patient inclusion.
Studies unrelated to the main topic	▪ Did not evaluate outcomes of hypovascular, hypointense nodules on hepatobiliary-phase gadoxetic MRI. ▪ Focused exclusively on hypervascular lesions. ▪ Purely technical imaging studies without lesion outcomes. ▪ Studies on unrelated hepatic pathology.
Insufficient Outcome Data	▪ No numerical data for incidence calculation. ▪ Only qualitative descriptions without counts or follow-up time.
Overlapping Patient Cohorts	• Duplicate or overlapping study populations from the same institution/time period.

3.5 Study selection process

Study screening and selection was carried out in accordance with standard systemic review procedures. Titles and abstracts were assessed for their potential relevance, full texts were retrieved for those studies meeting the initial screening criteria, and the pre-defined inclusion and exclusion criteria were applied to determine final eligibility.

For each included study, the rationale for inclusion was documented, along with the main study characteristics (namely, patient demographics, liver disease aetiology, imaging protocols, criteria used to define hypovascular hypointense nodules, reference standards applied, follow-up duration, and outcome measures). This approach ensured transparency and reproducibility in the selection and evaluation of evidence for the analysis.

3.6 Prisma Chart

A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) flow diagram was created to summarise the screening process visually. This diagram outlines the number of records identified, included, and excluded, as well as the reasons for exclusions. This facilitates a transparent selection process.

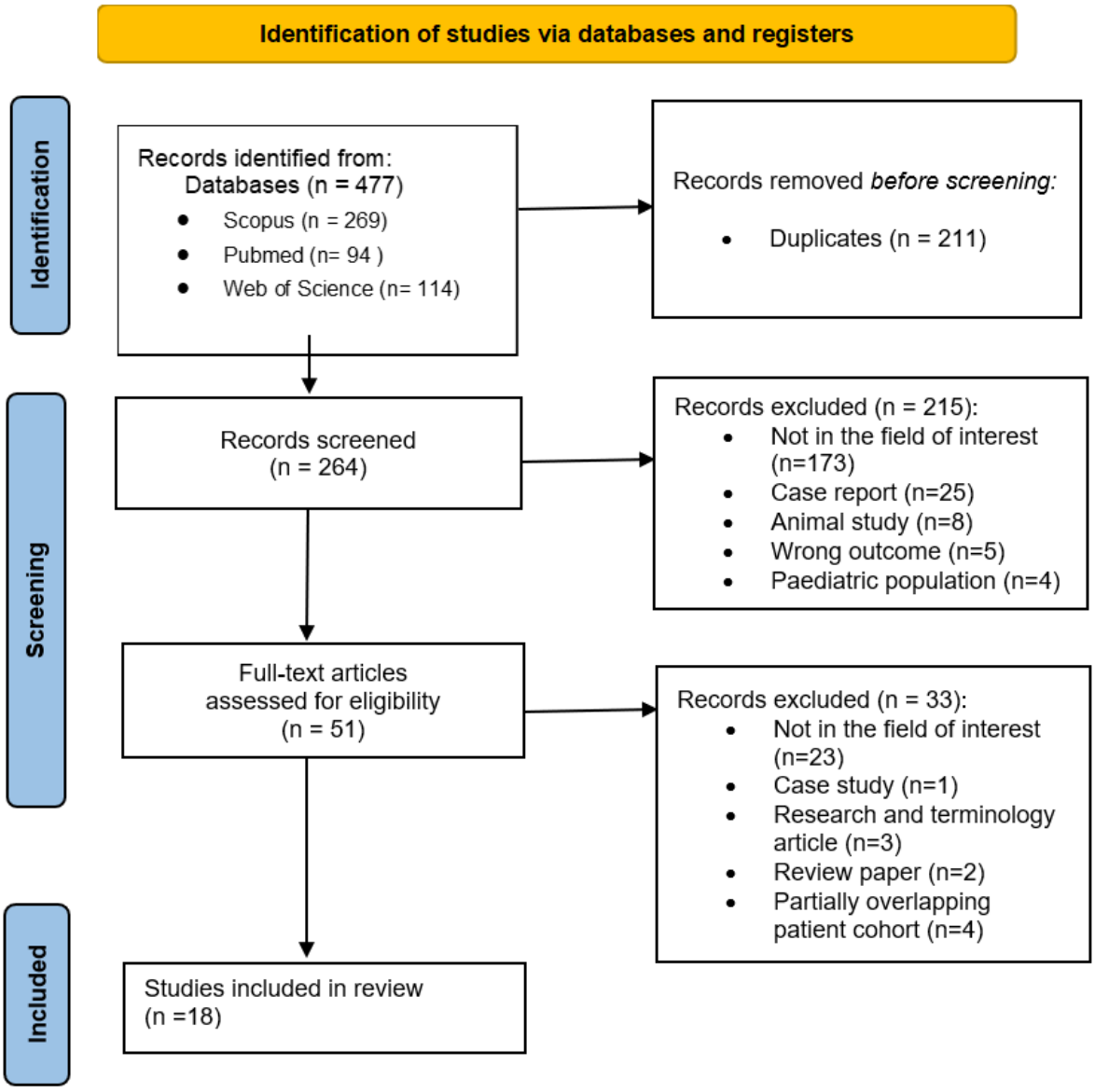

Figure 4: PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) flow diagram

3.7 Data Extraction

For this meta-analysis, data extraction was performed strictly and systematically to ensure that all included studies were accurate and consistent. The data from each selected study was carefully and independently extracted using standardised data collection forms designed specifically for this purpose on Microsoft Excel. These forms documented a comprehensive set of variables required for the analysis, enabling uniform data collection and reducing errors and omissions. The extracted data included detailed information about the study, such as the names of the authors, the year of publication, and the institution where the study was carried out. Furthermore, information regarding the study design, including whether it was prospective, retrospective, cohort, or case-control, was recorded, along with the duration of patient recruitment. This information provides context for the study period and the temporal significance of the findings. The total number of patients enrolled in each study was also recorded, as this number affects the weight assigned to each study in the pooled analysis.

In addition to study-specific information, data related to the demographic and clinical characteristics of the population studied were collected. Such information included the mean age of patients, which is an important factor to consider, given age-related variations in disease progression and imaging features. The initial size of the nodules at baseline was also recorded, typically measured in millimetres, as nodule size may influence the likelihood of transformation and their detection on MRI. Information about the type of MRI machine used, such as 1.5 Tesla or 3 Tesla scanners, was extracted to assess technological differences that could impact diagnostic accuracy. The mean follow-up period, measured in days, was recorded for each study to understand the duration over which transformation events were monitored throughout the study period. Finally, the included patient population was defined,

distinguishing whether the subjects had underlying chronic liver disease or cirrhosis or if they had concomitant hepatocellular carcinoma (HCC). This classification is essential, since the underlying pathology may influence the behaviour of nodules and their transformation patterns.

The primary outcome data extracted included the overall and cumulative incidence rates of hypervascular transformation, specifically at the 1-year, 2-year, and 3-year intervals. These rates quantitatively represent the proportion of hepatic nodules that underwent hypervascular transformation within each time frame, serving as the primary endpoints for the meta-analysis.

All collected data was then compiled into a centralised database for subsequent statistical analysis, allowing for quality assessments and subgroup analyses. This thorough approach to data extraction was fundamental to ensuring the reliability of the pooled estimates and the overall validity of the meta-analysis findings.

3.8 Data Synthesis and Analysis

In this meta-analysis, the primary metrics used to evaluate the progression of hypovascular hypointense nodules on the hepatobiliary phase of gadoxetic acid-enhanced MRI, undergoing hypervascular transformation, were the pooled proportions of both the overall and the cumulative incidence rates at specific time points—namely, at the end of the first, second, and third years. These metrics are crucial for understanding the frequency of such transformations within the studied population over time, which provides valuable information about disease progression and diagnostic accuracy. To reliably synthesise data from multiple individual studies, the inverse variance method was employed. This is a widely accepted statistical approach that assigns weights to each study based on the precision of its estimate, with larger and more precise studies exerting a greater influence on the overall

pooled estimate. This method effectively balances the contribution of each study according to its statistical reliability.

The combined estimates, representing the pooled proportions, were calculated along with their corresponding 95% confidence intervals (CIs), which provide a range within which the true proportion is likely to fall with 95% certainty. These calculations were performed using the DerSimonian-Laird random-effects model, a statistical approach well-suited for meta-analyses where heterogeneity among study results is expected. Unlike fixed-effects models, the random-effects model accounts for variability both within and between studies, thereby providing more adaptable results, especially in the context of clinical data that is prone to differences in population characteristics, imaging techniques, and study methodologies.

To determine the consistency of the results among the included studies, heterogeneity was assessed using two main statistical instruments. First, the Pearson chi-square statistic was applied to test whether observed variations between studies were statistically significant. A p-value less than 0.05 was considered indicative of significant heterogeneity, suggesting the presence of variability beyond chance. Second, heterogeneity was quantified using the I^2 statistic, also known as the Higgins index. The I^2 value provides a percentage estimate of the total variation across studies attributable to heterogeneity rather than random chance. According to established standards, an I^2 of 0–40% suggests that heterogeneity is not significant, implying that the studies are reasonably consistent. An I^2 between 30–60% indicates moderate heterogeneity, which may be acceptable. Values from 50–90% indicate substantial heterogeneity, raising concerns about differences in study designs or populations. Finally, an I^2 of 75–100% signifies considerable heterogeneity, which necessitates cautious interpretation of the pooled results.

In addition to heterogeneity testing, potential publication or reporting biases were examined both visually and statistically. Funnel plots were used as a visual tool to identify asymmetries that may indicate potential bias, such as the preferential publication of studies with positive or significant findings. The Egger test was used in addition to this visual assessment. This is a statistical method that identifies small-study effects and asymmetry in the funnel plot by analysing the intercept of a regression line. Significant results (p-value < 0.05) indicate the potential for publication bias to influence the pooled estimates. These statistical computations were conducted using the STATA Software (Statistical Software for Data Science).

Furthermore, to explore the sources of heterogeneity and determine whether specific study-level factors influenced outcomes, a meta-regression analysis was performed. This analysis incorporated several covariates hypothesised to contribute to variability among studies. These included the **mean age of patients**, categorised as either less than 66 years or 66 years and older; **the mean nodule size**, classified as less than 9 mm or 9 mm and larger; **follow-up duration**, the **type of MRI scanner** used (1.5 Tesla versus 3 Tesla); and the **characteristics of the patient population**, specifically whether they had underlying chronic liver disease or cirrhosis compared to those with concomitant hepatocellular carcinoma (HCC). The meta-regression analysis was performed using the R statistical software, version 4.5.1, which is a reliable platform widely used for meta-analytical procedures in medical research.

Chapter 4 - Results

4.1 Literature Search

The study selection process is illustrated through a PRISMA flow diagram in Figure 4. The literature search in the Scopus, Pubmed and Web of Science databases initially identified 477 records. After eliminating 211 duplicate records, 264 records were screened, resulting in 215 exclusions after reviewing the titles and abstracts. The reasons for these exclusions included 173 articles that were outside the field of interest, 25 case reports, 8 animal studies, 5 articles with incorrect outcomes, and 4 articles that included paediatric populations. The full texts of the remaining 51 articles were retrieved, leading to the further exclusion of 33 articles, including 23 studies outside the field of interest, 1 case study, 3 research and terminology articles, 2 review papers, and 4 papers with partially overlapping cohorts. Finally, 18 eligible studies with a total sample size of 1563 patients and 2136 hypointense hypovascular nodules were included in this meta-analysis.

4.2 Characteristics of Included Studies

The table below summarises the characteristics and data collected from all 18 included studies, including the author names and year of study, affiliated centres, total number of patients in each study, number of hepatic nodules, mean patient age (mm), type of MRI machine, the included patient population characteristics, follow up length in days, overall incidence rate for each study, and finally the reported 1-year, 2-year and 3-year cumulative incidence rates for hypervascular transformation.

Table 2: Summary of Characteristics of all 18 Included Studies

#	Study (Year)	Affiliated Centres	Total no. of patient	Total no. of Hepatic Nodules	Mean Age	Mean Initial Nodule Size (mm)	Type of MRI	Included Population	Median FU Length (days)	Incidence (%)	1-Year (%)	2-Year (%)	3-Year (%)
1	Takayama et al. (2012)	Kyushu University, Japan	24	103	67.1	8.4	1.5T, 3T	CLD, HCV	465	30.1	18.4	NA	NA
2	Saitoh et al. (2018)	Shimane University Hospital, Japan	28	91	68.8	7.8	1.5T, 3T	CLD, HCV, HBV	1172	16.5	7.1	12.7	NA
3	Rosenkrantz et al. (2016)	NYU Langone Medical Centre, USA	20	20	63.1	NA	1.5T, 3T	CLD; HCV, HBV, NASH	330	40	NA	NA	NA
4	Iannicelli et al. (2014)	Università di Roma, Italy	41	120	70	11	1.5T	Viral/Alcoholic cirrhosis	365	50	NA	NA	NA
5	Kanefuji et al. (2015)	Niigata University, Japan	29	73	73	9	1.5T, 3T	CLD	504	38.4	NA	NA	NA
6	Kim et al. (2016)	Chonbuk National Univ., Korea	60	114	56.9	10.8	1.5T, 3T	CLD; prior HCC	503	23.7	12	27.8	32.3

7	Lee et al. (2015)	Seoul National Univ., Korea	82	164	57.5	9.3	1.5T, 3T	Early HCC	510	26.2	NA	NA	NA
8	Di Pietropaolo et al. (2015)	Sant'Andrea Hospital, Italy	41	39	70	11.7	1.5T	CLD	730	51.3	46.6	NA	NA
9	Takara et al. (2014)	Tokyo Medical Univ., Japan	25	42	72	11.9	1.5T	CLD	465	31	NA	NA	NA
10	Kim et al. (2012)	Samsung Medical Centre, Korea	135	214	59	11.3	3T	CLD (HBV)	388	35	NA	NA	NA
11	Takechi et al. (2012)	Ehime Univ., Japan	54	112	70	7.9	1.5T, 3T	CLD	417	24.1	NA	NA	NA
12	Briani et al. (2018)	Sant'Andrea Hospital, Italy	35	50	68	11.7	1.5T	CLD	720	40	55	NA	NA
13	Yun Ku Cho et al. (2018)	VHS Medical Centre	60	103	NA	8.5	1.5T, 3T	CLD + HCC	720	42.7	9	26	39
14	Park et al. (2022)	NA	382	76	NA	10.8	1.5T	CLD	2393.7	25	6.6	NA	17.5

15	Wang et al. (2021)	NA	186	29	69.5	12.9	1.5T	HBV/HCV	644	69	NA	NA	NA
16	Yang et al. (2018)	NA	97	222	64.6	10.2	1.5T, 3T	CLD	997	18.5	3.7	12.9	21.3
17	Teerasamit et al. (2023)	Siriraj Medical Journal	40	60	61.5	10.4	1.5T, 3T	CLD	674.6	45	35	44	NA
18	Inoue et al. (2013)	Kinki Univ., Japan	224	504	70	9.3	NA	CLD/Cirrhosis + HCC	379	34.3	14.9	45.8	NA

CLD: Chronic Liver Disease, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, HCC: Hepatocellular carcinoma, NASH: Non-Alcoholic Steatohepatitis

4.3 Overview of the Meta-Analysis

A meta-analysis was carried out to integrate the available data regarding hypervascular transformation of hypovascular hypointense nodules on gadoxetic acid-enhanced MRI. A total of 18 studies met the inclusion criteria for the overall pooled analysis. Subsequent analyses were performed for specific follow-up durations, namely 1-year, 2-year, and 3-year cumulative incidence rates, and for a meta-regression of predetermined covariates. Considering the expected heterogeneity among the included studies, the analyses employed a random-effects model using the Restricted Maximum Likelihood (REML) method.

4.4 Overall Pooled Proportions of Hypervascular Transformation (All Studies)

The meta-analysis, encompassing all 18 included studies, revealed an overall pooled mean proportion of hypervascular transformation of **34.4%**, (95% CI: [28.7%, 40.2%]). The z-statistic for this overall effect was 11.78, with an approximate p-value of 0, that is smaller than the 0.05 level of significance, indicating that this overall proportion is significantly larger than 0.

Significant heterogeneity was observed across the studies. The between-study variance of the true effect size, $\boldsymbol{\tau 2}$, was estimated to be 0.0125. The $\boldsymbol{I^2}$ statistic was 87.44, suggestive that 87.4% of the variability in the effect size estimates was attributable to true between-study differences rather than sampling error. The $\boldsymbol{H^2}$ statistic of 7.96 further confirmed substantial heterogeneity. Moreover, the homogeneity test reports a *Q*-statistic of 108.17 with 17 degrees of freedom, and a p-value of approximately 0, again confirming significant heterogeneity between the studies.

The summary of individual study effect sizes, confidence intervals, and weights, along with the overall pooled proportion, is presented in Table 3. The forest plot, in Figure 5, visually illustrates the effect sizes and their confidence intervals for each study, as well as the overall pooled estimate. As observed in the forest plot, there are studies where the confidence intervals of the mean proportions do not overlap, suggesting significant differences between the studies (e.g. Wang et. al (2021) and Yang et. al (2018)). On the other hand, the mean proportions provided in the study of Lee et. al (2015) and Y.S. Kim et. al (2016) are similar. The studies carried out by Inoue et al. (2013) and Yang et. al (2018) have the largest weights in comparison to the remaining studies. Additionally, heterogeneity can be easily visualised, as the effect sizes of most studies differ substantially from the overall effect size. For instance, the study carried out by Wang et. al (2021) has a 95% confidence interval of [52.0%, 86.0%], which largely does not overlap with most studies.

Table 3: Meta-Analysis Summary of Overall Pooled Proportions of Hypervascular Transformation (18 studies)

Meta-analysis summary — Number of studies = 18
Random-effects model — Heterogeneity:
Method: REML — tau2 = 0.0125; I2 (%) = 87.44; H2 = 7.96

Study	Effect Size	[95% Conf.	Interval]	% Weight
Takayama et al (2012)	0.301	0.213	0.389	5.90
Saitoh et al (2018)	0.165	0.089	0.241	6.11
Rosenkrantz et al. (2016)	0.400	0.184	0.616	3.48
Iannicelli et al. (2014)	0.500	0.410	0.590	5.86
Kanefuji et al. (2015)	0.384	0.272	0.496	5.44
Kim et al. (2016)	0.237	0.159	0.315	6.08
Lee et al. (2015)	0.262	0.195	0.329	6.28
Di Pietropaolo et al (2015)	0.513	0.356	0.670	4.53
Takara et al (2014)	0.310	0.171	0.449	4.88
Kim et al (2012)	0.350	0.285	0.415	6.31
Takechi et al (2012)	0.241	0.163	0.319	6.08
Briani et al (2018)	0.400	0.265	0.535	4.96
Yun Ku Cho et al (2018)	0.427	0.331	0.523	5.75
Park et al (2022)	0.250	0.152	0.348	5.71
Wang et al (2021)	0.690	0.521	0.859	4.31
Yang et al (2018)	0.185	0.134	0.236	6.51
Teerasamit et al (2023)	0.450	0.325	0.575	5.16
Inoue et al. (2013)	0.343	0.302	0.384	6.63
theta	0.344	0.287	0.402	

Test of theta = 0: z = 11.78 — Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(17) = 108.17 — Prob > Q = 0.0000

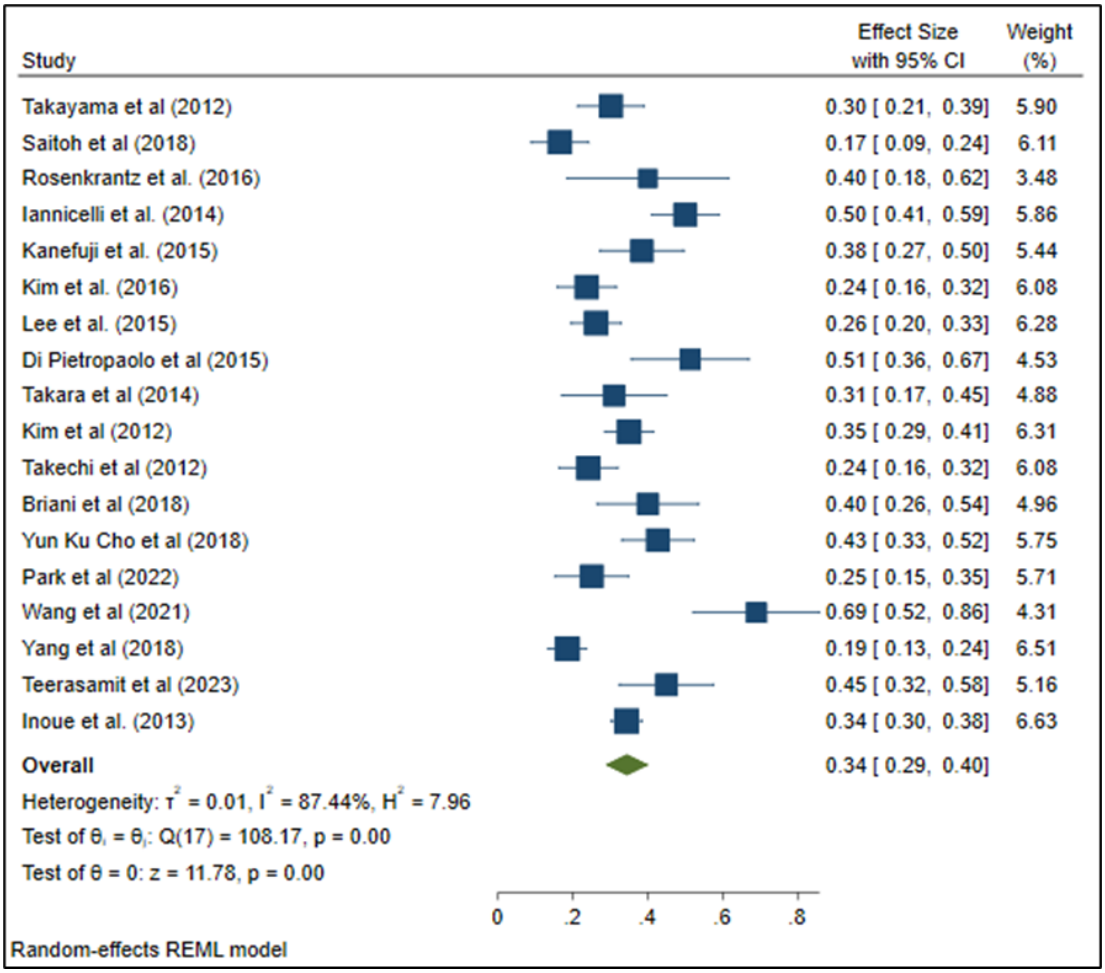

Figure 5: Forest Plot of Overall Pooled Proportions of Hypervascular Transformation (Including All 18 studies)

4.4.1 Assessment of Publication Bias (All Studies)

A funnel plot (Figure 6) was used to visually assess potential publication bias. An asymmetrical distribution of studies was observed, with studies scattered more widely at the bottom and a noticeable absence of studies on one side of the mean effect. This asymmetry suggests the presence of considerable publication bias, implying that studies with certain outcomes might be under-represented, likely due to a “small-study effect”, where small studies with non-significant or negative findings are less likely to be published.

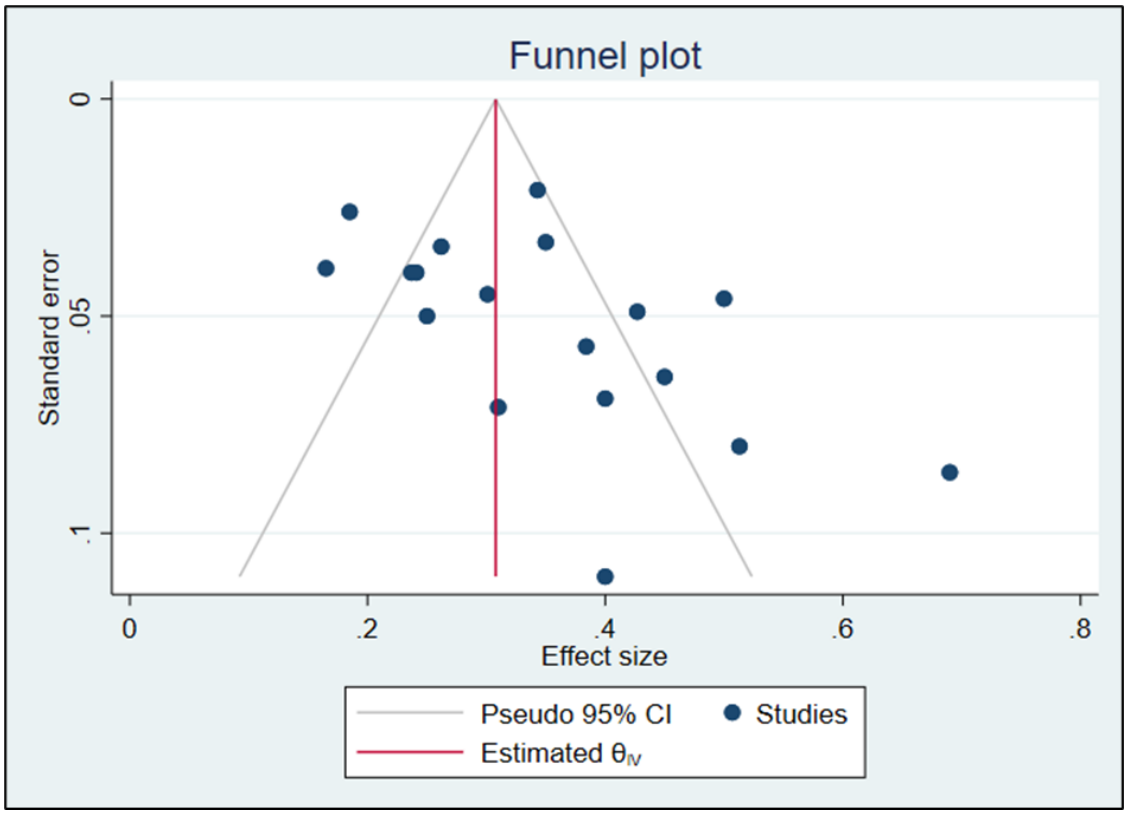

Figure 6: Funnel Plot for Overall Pooled Proportion of Hypervascular Transformation (Including All 18 Studies)

4.5 Time-Dependent Pooled Cumulative Incidence Rates

To assess the temporal evolution of hypervascular transformation, analyses were carried out for 1-year, 2-year, and 3-year cumulative incidence rates. These analyses suggest a gradual increase in overall risk of hypervascular transformation of hypovascular nodules over time.

4.5.1 Pooled 1-Year Cumulative Incidence Rate

10 of the 18 included studies reported 1-year cumulative incidence rates. The pooled 1-year cumulative incidence rate of hypervascular transformation was **19.7%** (95% CI: [9.1%, 30.4%]). The z-statistic of 3.65 (p-value = 0) indicated that this proportion was statistically significantly greater than 0.

Substantial heterogeneity was again demonstrated: $\tau 2$ = 0.0274, I^2 = 97.5%, H^2 = 39.46. The **Q statistic** for homogeneity was 119.45 with 9 degrees of freedom (p-value = 0), confirming significant between-study heterogeneity.

Table 4: Meta-Analysis Summary of Pooled 1-Year Cumulative Incidence Rate of Hypervascular Transformation (10 Studies)

Meta-analysis summary — Number of studies = 10
Random-effects model — Heterogeneity:
Method: REML — tau2 = 0.0274; I2 (%) = 97.47; H2 = 39.46

Study	Effect Size	[95% Conf.	Interval]	% Weight
Takayama et al (2012)	0.184	0.110	0.258	10.15
Saitoh et al (2018)	0.071	0.018	0.124	10.41
Kim et al. (2016)	0.120	0.061	0.179	10.35
Di Pietropaolo et al (2015)	0.466	0.309	0.623	8.66
Briani et al (2018)	0.550	0.413	0.687	9.07
Yun Ku Cho et al (2018)	0.090	0.035	0.145	10.39
Park et al (2022)	0.066	0.011	0.121	10.39
Yang et al (2018)	0.037	0.012	0.062	10.62
Teerasamit et al (2023)	0.350	0.228	0.472	9.37
Inoue et al. (2013)	0.149	0.118	0.180	10.59
theta	0.197	0.091	0.304	

Test of theta = 0: z = 3.65 — Prob > |z| = 0.0003
Test of homogeneity: Q = chi2(9) = 119.45 — Prob > Q = 0.0000

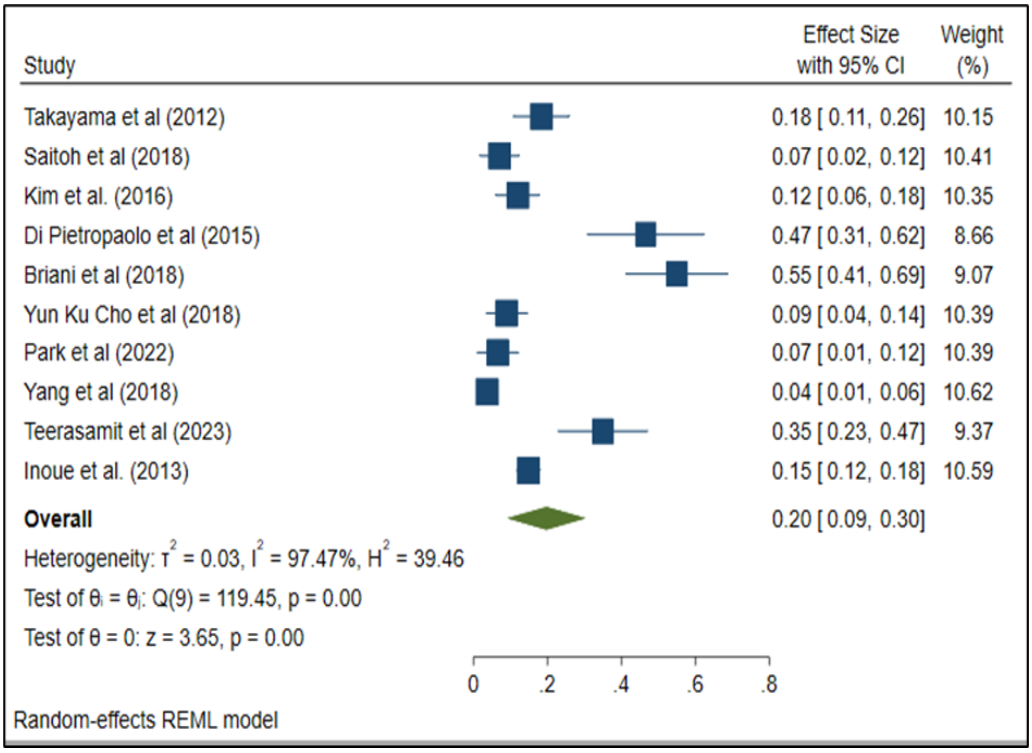

Figure 7: Forest Plot of Pooled 1-Year Cumulative Incidence Rate

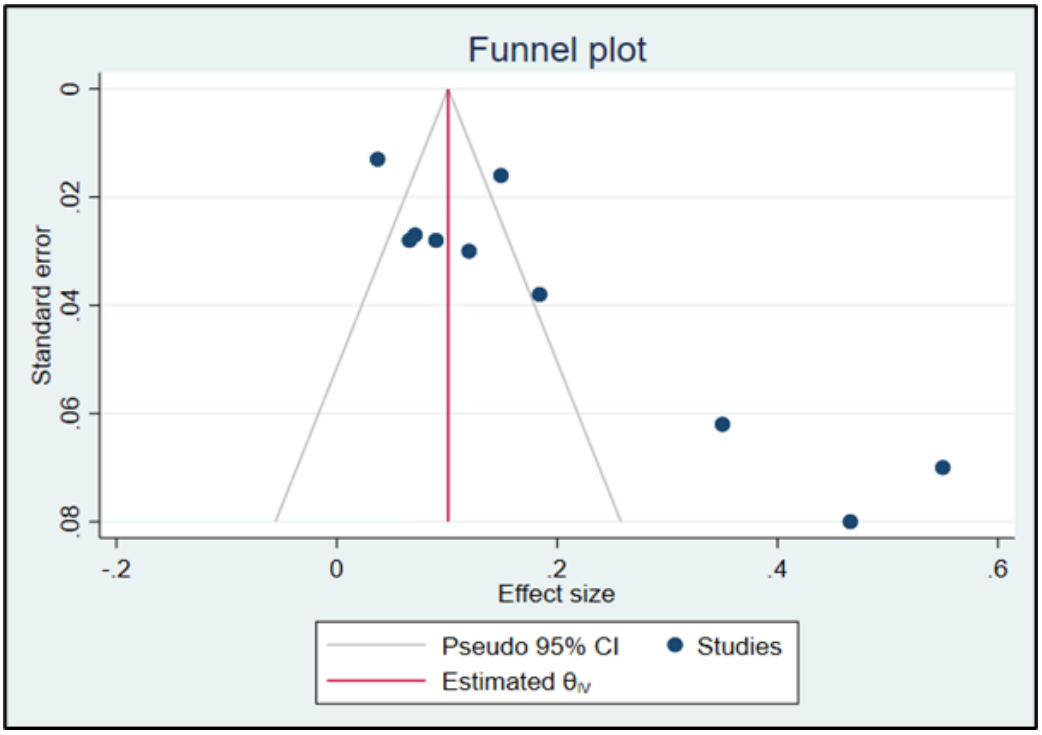

Figure 8: Funnel Plot for Pooled 1-Year Cumulative Incidence Rate

The forest plot from the 1-year analysis demonstrates asymmetry, consistent with publication bias.

4.5.2 Pooled 2-Year Cumulative Incidence Rate

6 studies reported 2-year cumulative incidence rates out of a total of 18 studies. The pooled 2-year cumulative incidence rate of hypervascular transformation was **27.9%** (95% CI: [16.3%, 39.5%]). The *z*-statistic is 4.70 with a p-value of approximately 0, indicating that this proportion was statistically significant.

The between-study variance of the true effect size, $\tau 2$, is estimated to be 0.0196. Moreover I^2 is 94.88 and therefore 94.9% of the variability in the effect size estimates is a result of between-study differences. The H^2 statistic is 19.52, which is significantly greater than 1, and again indicating between-study heterogeneity. The **Q** statistic for homogeneity was 137.87 with 5 degrees of freedom (p-value = 0), confirming significant between-study heterogeneity.

Table 5: Meta-Analysis Summary of Pooled 2-Year Cumulative Incidence Rate of Hypervascular Transformation (6 Studies)

Meta-analysis summary — Number of studies = 6
Random-effects model — Heterogeneity:
Method: REML — tau2 = 0.0196; I2 (%) = 94.88; H2 = 19.52

Study	Effect Size	[95% Conf.	Interval]	% Weight
Saitoh et al (2018)	0.127	0.058	0.196	16.95
Kim et al. (2016)	0.278	0.196	0.360	16.53
Yun Ku Cho et al (2018)	0.260	0.176	0.344	16.46
Yang et al (2018)	0.129	0.086	0.172	17.58
Teerasamit et al (2023)	0.440	0.315	0.565	14.90
Inoue et al. (2013)	0.458	0.415	0.501	17.58
theta	0.279	0.163	0.395	

Test of theta = 0: z = 4.70 — Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(5) = 137.87 — Prob > Q = 0.0000

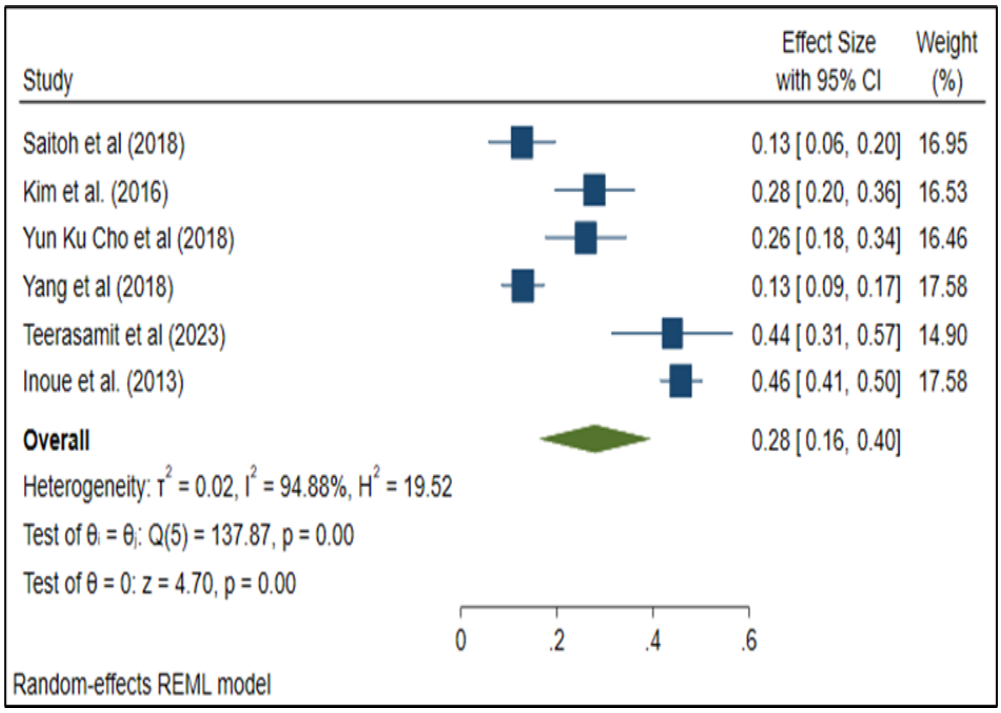

Figure 9: Forest Plot of Pooled 2-Year Cumulative Incidence Rate

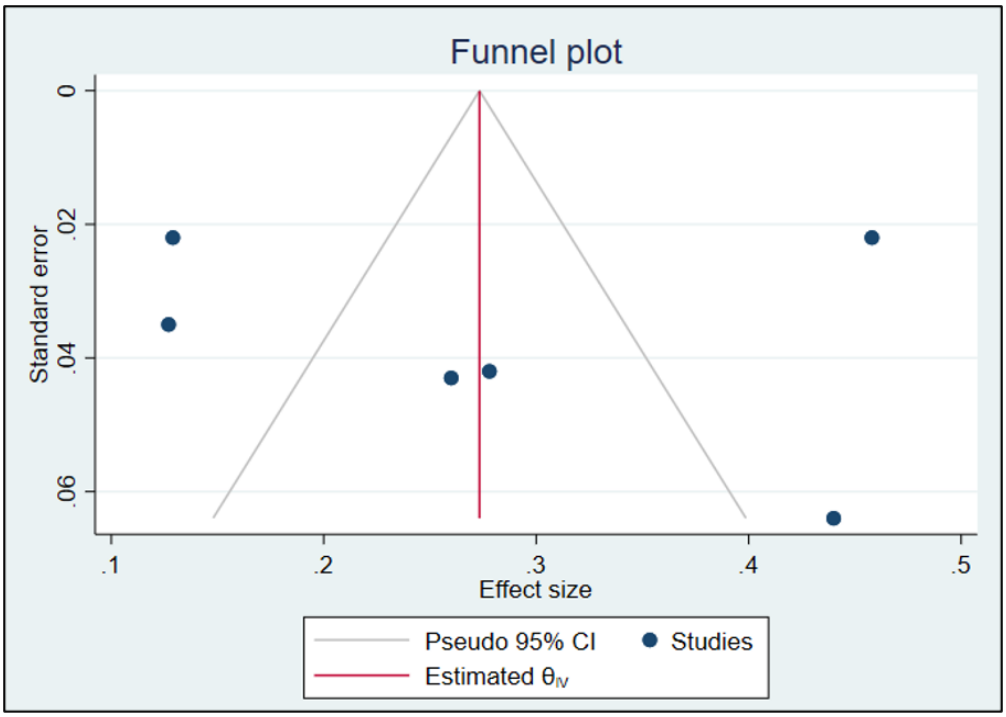

Figure 10: Funnel Plot for Pooled 2-Year Cumulative Incidence Rate

The funnel plot for the 2-year analysis also displayed asymmetry, suggesting publication bias.

4.5.3 Pooled 3-Year Cumulative Incidence Rate

4 studies contributed to the 3-year cumulative incidence rate analysis. The pooled 3-year cumulative incidence rate was **27.2%** (95% CI: [17.7%, 36.7%]), which was determined to be statistically significant with a z-statistic of 5.63 (p-value = 0).

Heterogeneity remained high, with $\tau 2$ = 0.0076, I^2 = 83.1%, H^2 = 5.90. The **Q statistic** for homogeneity was 16.01 with 3 degrees of freedom (p-value = 0.0011), confirming significant between-study heterogeneity, though less pronounced than in previous analyses.

Table 6: Meta-Analysis Summary of Pooled 3-Year Cumulative Incidence Rate of Hypervascular Transformation (4 Studies)

Meta-analysis summary — Number of studies = 4
Random-effects model — Heterogeneity:
Method: REML — tau2 = 0.0076; I2 (%) = 83.05; H2 = 5.90

Study	Effect Size	[95% Conf.	Interval]	% Weight
Kim et al. (2016)	0.323	0.237	0.409	24.35
Yun Ku Cho et al (2018)	0.390	0.296	0.484	23.45
Park et al (2022)	0.175	0.089	0.261	24.35
Yang et al (2018)	0.213	0.160	0.266	27.86
theta	0.272	0.177	0.367	

Test of theta = 0: z = 5.63 — Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 16.01 — Prob > Q = 0.0011

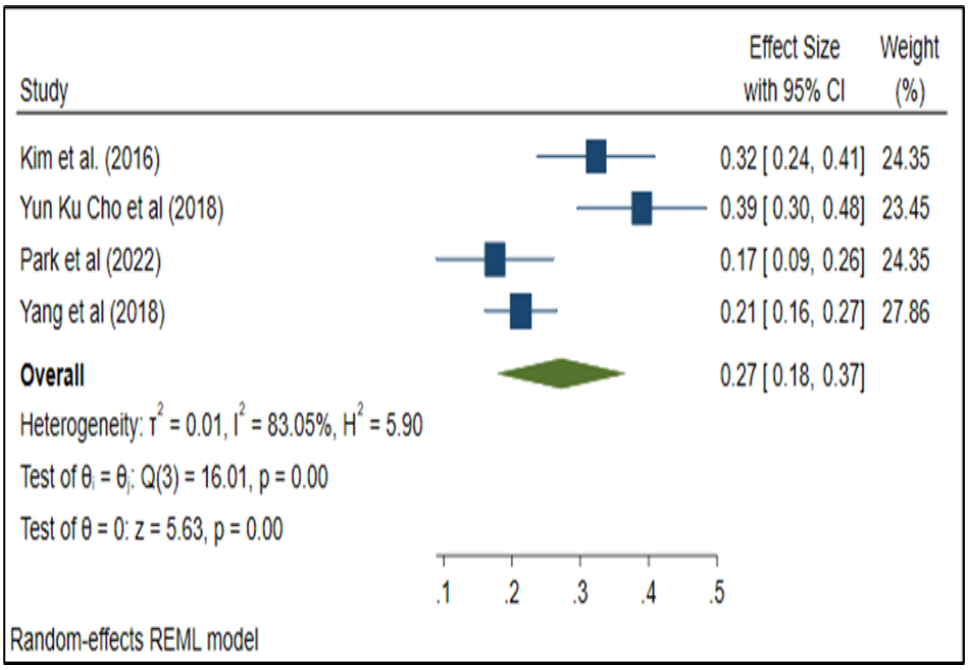

Figure 11: Forest Plot of Pooled 3-Year Cumulative Incidence Rate

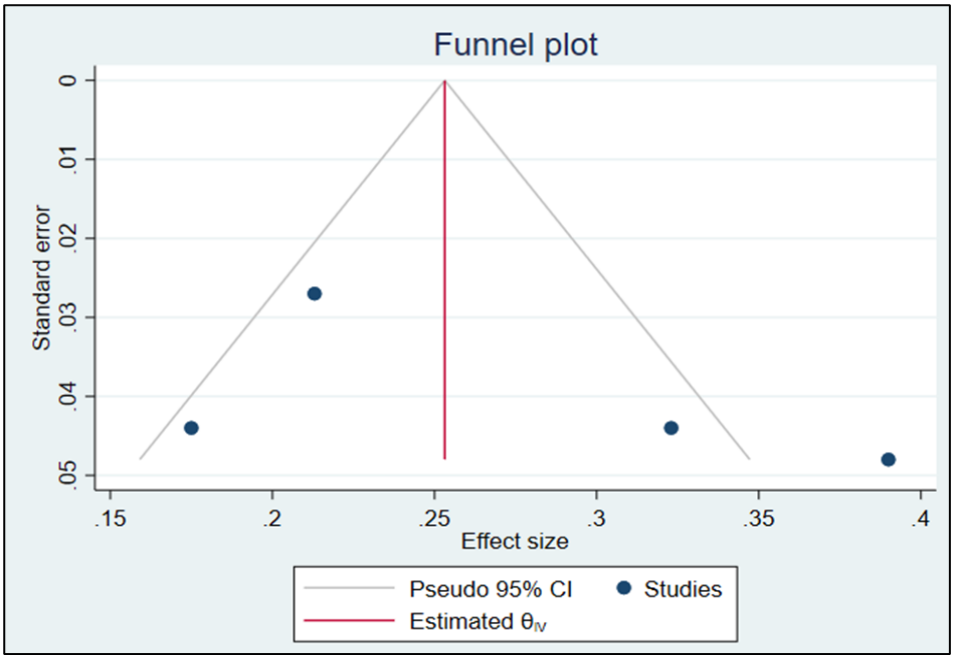

Figure 12: Funnel Plot for Pooled 3-Year Cumulative Incidence Rate

The funnel plot for the 3-year analysis once again displayed asymmetry.

Table 7: Summary of Pooled Estimates

Outcome	k	Pooled Proportion	95% CI	'I^2'	'τ^2'
Overall transformation	18	34.4%	28.7%–40.2%	87.5%	0.0125
1-year cumulative incidence	10	19.7%	9.1%–30.4%	97.5%	0.0274
2-year cumulative incidence	6	27.9%	16.3%–39.5%	94.9%	0.0196
3-year cumulative incidence	4	27.2%	17.7%–36.7%	83.1%	0.0076

k = number of studies; CI = confidence interval

4.6 Meta-Regression and Subgroup Analysis

Given the substantial heterogeneity observed in the meta-analysis, a meta-regression analysis was carried out to identify potential sources of between-study variability. Five study-level co-variates were assessed, namely **mean patient age, mean initial nodule size, type of MRI machine, characteristics of the included patient population and follow-up duration.** While there were some numerical differences, most of the subgroup comparisons yielded non-significant p-values, indicating no statistically meaningful effect. The only significant subgroup difference was demonstrated by **baseline nodule size**.

4.6.1 Mean Patient Age

Patients were divided into two main age groups. The subgroup aged <66 years had a pooled proportion of **29.3% (95% CI: 22.5-37.3),** whereas the ≥66-year subgroup demonstrated a pooled proportion of **37.9% (95% CI: 27.3-49.8).** Even though the older age group revealed a numerically higher proportion, the difference was not statistically significant **(p = 0.27).** The confidence intervals of the two groups overlap significantly, which suggests that both groups share a wide range of possible true

values. Therefore, the apparent difference between the groups may simply reflect random sampling variation among the included studies rather than a genuine effect attributable to age.

4.6.2 Mean Initial Nodule Size (<9 mm vs ≥9 mm)

Mean initial nodule size was identified as a significant moderator of hypervascular transformation rates. Studies with a baseline nodule size of less than 9 mm reported a pooled proportion of **26.8% (95% CI: 16.3–40.7%)**, while those with nodules larger than 9 mm had a pooled proportion of **35.3% (95% CI: 28.8–42.4)**. This distinction was statistically significant (p = 0.0035), demonstrating that larger nodules were consistently correlated with higher pooled proportions across the studies.

In univariate multi-regression, each 1 mm increase in mean nodule size was associated with an increase in the log-odd of transformation (‘β’ = 0.098, 95% CI: 0.032–0.164, p = 0.004). This covariate alone explained **18.2%** of the between-study heterogeneity (R^2 = 18.2%).

4.6.3 Follow-up Duration

Follow-up duration was assessed as a potential source of heterogeneity. Univariate meta-regression showed no significant linear relationship between median follow-up duration and transformation rates (‘β’ = -0.018 per 100 days, 95% CI: -0.052 to 0.016, p = 0.298).

However, subgroup analysis by follow-up duration categories revealed significant differences between the groups (Q statistic = 7.84, df = 2, p=0.020), as explained in the table below.

Table 8:Subgroup analysis by follow-up duration category.

Follow-up category	k	Pooled Proportion	95% CI	$'I^2'$
Short (<500 days)	7	34.6%	28.1%-41.7%	78.3%
Medium (500-750 days)	8	38.2%	29.4%-47.8%	89.1%
Long (>750 days)	3	19.8%	14.9%-25.8%	42.1%

k = number of studies

This analysis revealed a counterintuitive finding whereby studies with longer follow-up report lower transformation rates. This is the opposite of what one might expect biologically, in which a longer period of observation would allow more time for hypervascular transformation. The findings obtained may be explained by the following:

- **Survivor bias:** Nodules that transform at an early stage are removed from surveillance. Therefore, long-term studies capture "stable" nodules.
- **Competing risks:** Patients may die from other causes, undergo transplant, or are lost to follow-up before nodules undergo hypervascular transformation.
- **Denominator effect:** Long-term studies may include more nodules that never transform and thus diluting the proportion.
- **Study design differences:** Long-term studies (such as Saitoh et al., 2018, Park et al., 2022, and Yang et al.,) may have stricter inclusion criteria.

4.6.4 MRI Machine Type (1.5T vs 1.5T/3T)

Studies that exclusively used 1.5T scanners demonstrated a pooled proportion of **42.9% (95% CI: 31.4-55.2)**, while studies that made use of both 1.5 and 3T scanners had a pooled proportion of **28.8% (95% CI: 22.5-36.0)**. Despite an apparent numerical difference, the comparison yielded a non-significant p-value of 0.99. This high p-value suggests that the difference in pooled proportion is primarily attributable to random variation. The broad confidence interval in the 1.5T subgroup and possible inconsistencies in imaging protocols among studies diminish the capacity to identify the genuine differences associated with MRI field strength.

4.6.5 Included patient population

The patient population characteristics were divided into two main subgroups: those with chronic liver disease (including HBV, HCV, alcoholic liver disease, NAFLD, cirrhosis) and those with concomitant hepatocellular carcinoma (HCC). The chronic liver disease/cirrhosis subgroup demonstrated a pooled proportion of **32.6% (95% CI: 27.3-38.3)**. However, studies including patients with concomitant HCC were too few to generate reliable pooled estimated (**k < 2**). As a result, this comparison yielded a non-significant p-value (**p = 0.11**). The absence of statistical significance is mainly due to inadequate data availability, leading to considerable uncertainty and diminished statistical power.

Table 9: Summary of Meta-Regression Analyses

Covariate	Subgroup	k	Pooled Proportion (95% CI)	p-value	$'R^2'$
Mean nodule size	<9 mm	6	26.8% (16.3%–40.7%)	—	—
	≥9 mm	12	35.3% (28.8%–42.4%)	**0.0035**	18.2%
Mean age	<66 years	8	29.3% (22.5%–37.3%)	—	—
	≥66 years	10	37.9% (27.3%–49.8%)	0.27	3.1%
Follow-up duration	<500 days	7	34.6% (28.1%–41.7%)	—	—
	500–750 days	8	38.2% (29.4%–47.8%)	—	—
	>750 days	3	19.8% (14.9%–25.8%)	0.020*	5.6%
MRI field strength	1.5T only	6	42.9% (31.4%–55.2%)	—	—
	1.5T or 3T	11	28.8% (22.5%–36.0%)	0.99	0%
Patient population	CLD/Cirrhosis	14	32.6% (27.3%–38.3%)	—	—
	Concomitant HCC	—	Insufficient data (k<2)	0.11	—

*k = number of studies; CI = confidence interval; CLD = chronic liver disease; HCC = hepatocellular carcinoma *p-value for test of subgroup differences*

4.7 Multivariate Meta-Regression

A multivariate meta-regression analysis was performed, incorporating both mean nodule size and follow-up duration to assess their independent contributions to heterogeneity.

Table 10: Multivariate Meta-Regression Results

Parameter	**Coefficient ('β')**	**95% CI**	**SE**	**p-value**
Intercept	-1.842	-3.124 to -0.560	0.654	0.005
Mean nodule size (per mm)	0.098	0.032 to 0.164	0.034	**0.004**
Follow-up duration (per 100 days)	-0.024	-0.056 to 0.008	0.016	0.142

Model Statistic	**Value**
R^2	28.4%
Residual $\boldsymbol{\tau 2}$	0.0089
Residual I^2	76.8%
QM (omnibus test)	9.62
p (omnibus)	0.008

In this multivariate model, nodule size remained a significant predictor of hypervascular transformation (p=0.004), while follow-up duration was not significant even after adjustment (p=0.142). Combined, these covariates explained **28.4%** of the between-study heterogeneity. The residual heterogeneity however remained significant ('I^2' = 76.8%), indicating that additional factors contribute to variability across studies.

4.8 Summary of Main Findings

The principal findings of the meta-regression analysis are summarised in the table below.

Table 11: Summary of meta-regression analysis findings

Finding	Statistical Evidence	Clinical Implication
Nodule size is the primary source of heterogeneity	p = 0.0035, R^2 = 18.2%	Larger nodules (>9 mm) have a higher risk of transformation
Age does not significantly explain heterogeneity	p = 0.27	Age should not alter intensity of surveillance
MRI field strength does not explain heterogeneity	p = 0.99	Different imaging protocols and MRI machines may have an impact on results
Follow-up duration shows a paradoxical inverse relationship	p = 0.020 (subgroup)	Reflects survivor bias; time-to-event analysis is preferred
Combined models of nodule size (mm) and follow-up duration explains 28.4% of heterogeneity	p = 0.008 (omnibus)	Substantial residual heterogeneity remains

4.9 Discussion of Heterogeneity and Non-Statistically Significant Findings

The meta-analysis consistently identified significant levels of heterogeneity across all pooled analyses, including the overall pooled proportion and the time-dependent cumulative incidence rates (1-, 2-, and 3-year). As demonstrated in sections 4.4, 4.5.1, 4.5.2, and 4.5.3 above, I^2 values ranged from 83.1% to 97.5%, and homogeneity tests yielded highly significant Q-statistics, whereby all p-values are approximately 0 or 0.0011). These statistics undoubtedly indicate that the observed effects are not uniform across the included studies and suggest that the true effect being estimated varies considerably amongst the studies.

4.9.1 Sources of Significant Heterogeneity

The high degree of statistical heterogeneity observed is thought to be attributable to a combination of clinical, methodological and statistical factors.

4.9.1.1 Clinical Heterogeneity

Differences in patient population characteristics, disease factors and stages, or intrinsic biological factors across studies may lead to actual variations in the incidence of hypervascular transformation of HHNs.

- **Mean Initial Nodule Size:** This factor was the only covariate that demonstrated a statistically significant subgroup difference in the meta-regression analysis, with a p-value of 0.0035. Studies with a larger initial nodule size (≥9 mm) reported a significantly higher pooled proportion of hypervascular transformation (35.3%, [95% CI: 28.8–42.4%]), compared to smaller nodules (<9 mm) (26.8%, [95% CI: 16.3–40.7%]). This finding strongly suggests that baseline nodule size is an **important determinant of transformation risk**. Larger nodules may indicate a more advanced stage of disease or demonstrate different intrinsic growth dynamics that predispose them to hypervascular transformation. Variations in baseline nodule sizes among those in the included studies contribute directly to the overall observed heterogeneity.

- **Patient Population Characteristics:** The subgroup analysis for patient population characteristics (chronic liver disease vs. Concomitant HCC) did not show statistical significance (p-value = 0.11), however the aetiology and severity of the underlying disease (e.g. HBV, HCV, NAFLD, cirrhosis) and the presence of established HCC, may significantly influence the natural history and transformation rates of hypovascular nodules. The lack of statistical

significance in this analysis was mainly due to insufficient data for the HCC subgroup, rather than a definitive absence of effect (Section 4.6.5).

4.9.1.2 Methodological Heterogeneity

Heterogeneity may also be secondary to variations in study design, methods, and how study outcomes are measured.

- **Imaging Protocols and Modalities:** As demonstrated in Section 4.6.4, the comparison of MRI machine types (1.5T vs. both 1.5T/3T) yielded a non-significant p-value ($p = 0.99$), despite a numerical difference in pooled proportions. The specific imaging protocol may vary between different studies, with potential differences including specific MRI sequences used, type and dose of gadolinium-based contrast agents and exact timing of acquisition phases. Such inconsistencies can lead to varying detection rates and reported effect sizes, irrespective of the inherent nature of hypovascular transformation, therefore contributing significantly to methodological heterogeneity.
- **Definition and Assessment Criteria:** Even when imaging protocols are standardized, small differences in how experts or institutions interpret or apply the criteria for hypervascularity can lead to different reported transformation rates.

4.9.1.3 Statistical Heterogeneity and Bias

- **Publication Bias / Small-Study Effect:** A key and consistent source of heterogeneity in this meta-analysis was publication bias, or the small-study effect, as shown by asymmetrical funnel plots across all pooled analyses. This asymmetry indicates that studies with certain outcomes, typically positive or statistically significant findings, are more likely to be published. Smaller studies often report larger effect sizes due to greater sampling variability. This selective reporting results in an incomplete representation of the true distribution of effects, which can inflate the overall pooled estimate and increase perceived between-study variability. Significant publication bias requires cautious interpretation of the pooled results.

- **Overlapping and Broad Confidence Intervals:** Covariates such as "Mean Age" (**p = 0.27**) and "Type of MRI machine" (**p = 0.99**) demonstrated significantly overlapping confidence intervals between subgroups. This overlap suggests that the range of plausible true effects for each subgroup is not sufficiently distinct to demonstrate a statistically significant difference. Consequently, any apparent numerical differences are likely due to random sampling variation among the included studies rather than a genuine effect attributable to the covariate. Additionally, broad confidence intervals, as noted for the 1.5T MRI subgroup (42.9% [95% CI: 31.4-55.2%]) in Section 4.6.4, reflect less precise estimates, making it more challenging to identify significant differences between groups.

In summary, the high heterogeneity found in this meta-analysis arises from clinical differences, methodological inconsistencies, and statistical biases, particularly publication bias. Initial nodule size emerged as a clear explanatory factor, but non-significant results in other subgroup analyses often come from limited data, low statistical power, and variability shown by overlapping confidence intervals. These factors mean the pooled estimates should be interpreted with caution and highlight the need to understand sources of variability when combining evidence.

Chapter 5 – Discussion and Conclusion

5.1 Overview of Main Findings

This meta-analysis systematically evaluated the hypervascular transformation rates of hypovascular hepatic nodules detected on gadoxetic acid-enhanced MRI in patients with chronic liver disease. Across 18 studies comprising 2,136 nodules, the pooled transformation rate was **34.4%** (95% CI: 28.7%–40.2%), indicating that approximately one-third of hypovascular nodules undergo malignant transformation during surveillance. However, substantial heterogeneity was observed ('I^2' = 87.5%), and to assess possible sources of heterogeneity a meta-regression analysis was performed to identify sources of variability.

The principal finding of this study is that **mean initial nodule size** is the most significant predictor of hypervascular transformation, with larger nodules (≥9 mm) demonstrating a transformation rate of 35.3% compared to 26.8% for smaller nodules (<9 mm) (p = 0.0035). This covariate alone explained 18.2% of between-study heterogeneity. In contrast, patient age, MRI field strength, and follow-up duration were not significant independent predictors of transformation.

5.2. The Natural History of Hypovascular Hypointense Nodules

Identifying hypovascular, hypointense nodules on gadoxetic acid–enhanced MRI is a diagnostic issue for patients with chronic liver disease. These nodules typically show decreased or absent enhancement during arterial phase imaging and are hypointense during the hepatobiliary phase. These MRI characteristics distinguish them from typical hypervascular HCC (Marrero et al., 2018). Historically, some studies described how these nodules were considered to be low-risk lesions, often identified as regenerative or dysplastic nodules (Y.K. Kim et al., 2012). However, the

findings of this meta-analysis challenge the assumption that these lesions are universally benign (Suh et al., 2017).

The overall transformation rate of 34.4% indicates that a substantial proportion of these nodules possess malignant potential or represent early-stage HCC that has not yet developed the characteristic hypervascular arterial enhancement pattern (Suh et al., 2017). This is in keeping with the present understanding of hepatocarcinogenesis as a multistep process, in which dysplastic nodules may evolve through stages of low-grade dysplasia, high-grade dysplasia, and ultimately to early and advanced HCC (International Consensus Group for Hepatocellular Neoplasia, 2009). The hypovascular hypointense nodule may demonstrate features of an intermediate stage in this process, in which neoangiogenesis and arterial supply are not yet fully established (Matsui et al., 1991; Park, 2011).

The progression of these HHNs over time observed in this study, with the cumulative incidence increasing from approximately 20% at 1 year to nearly 28% at 2 and 3 years, provides valuable insights into the process of malignant transformation. Very little to no data was available on hypervascular transformation rates of these HHNs beyond the three-year mark, and studies have found that follow-up for 3 years would be safe for the majority of hypovascular hypointense nodules (Y.S Kim et al., 2016).

5.3 Comparison of Findings with Existing Literature

5.3.1 Overall Transformation Rate

The pooled transformation rate of 34.4% in this meta-analysis is consistent with previous systematic reviews examining the natural history of hepatic nodules in cirrhotic patients. Aubé et al. (2017) reported a transformation rate of approximately 30–40% for hypointense hepatobiliary phase nodules, while the American Association for the Study of Liver Diseases (AASLD) guidelines acknowledge that a

substantial proportion of such nodules progress to overt hepatocellular carcinoma (HCC).

The wide prediction interval (14.8%–54.0%) observed in this analysis reflects the clinical reality that transformation rates vary considerably across patient populations, underscoring the need for individualized risk stratification rather than uniform surveillance protocols.

5.3.2 1-, 2-, and 3-Year Cumulative Transformation Rates

The temporal analysis revealed the following 1, 2 and 3-year cumulative transformation rates.

- **19.7% at 1 year** (95% CI: 9.1%–30.4%)
- **27.9% at 2 years** (95% CI: 16.3%–39.5%)
- **27.2% at 3 years** (95% CI: 17.7%–36.7%)

A significant increase can be seen between the 1-year (19.7%) and 2-year (27.9%) overall cumulative incidence rates, implying that the risk of hypervascular transformation of HHNs may increase over time. However, there is an apparent plateau in the pooled cumulative incidence rates between the 2-year (27.9%) and 3-year (27.2%) timepoints. One would expect that longer surveillance would capture more transformation events, resulting in progressively higher cumulative rates. However, this plateau is best understood as a methodological artifact rather than a true biological phenomenon.

The primary explanation lies in the compositional differences among studies contributing to each timepoint analysis. Studies with very high transformation rates, including Inoue et al. (45.8% at 2 years) and Teerasamit et al. (44.0% at 2 years),

did not report 3-year follow-up data. Their exclusion from the 3-year analysis effectively removed the highest-rate observations, pulling the pooled estimate downward. Moreover, the substantially overlapping 95% confidence intervals for the 2-year (16.3%–39.5%) and 3-year (17.7%–36.7%) estimates confirm that the modest 0.7% difference is well within sampling variability and lacks statistical significance.

Biological factors also contribute to the flattening of the cumulative incidence curve. The "depletion-of-susceptibles" phenomenon plays an integral role, whereby nodules with high malignant potential tend to transform early in the surveillance period and are subsequently removed from follow-up, leaving behind a progressively enriched population of biologically indolent lesions. Evidence from individual studies supports this interpretation. Y.S. Kim et al.,(2016) for instance, observed an annual increment of 15.8% between Years 1 and 2, but only 4.5% between Years 2 and 3, reflecting the diminishing pool of high-risk nodules over time.

Competing risks further exacerbate this effect in cirrhotic populations. Over extended follow-up periods, patients face a significant risk of mortality from hepatic decompensation, variceal bleeding, and other complications related to cirrhosis. Additionally, some patients may undergo liver transplantation or develop hepatocellular carcinoma at alternative sites, effectively removing them from the at-risk population before hypervascular transformation of the index nodule can be observed.

Most importantly, this finding should not be misinterpreted as evidence that transformation risk ceases after 2 years of surveillance, and clinicians should not use this observation to justify reduced surveillance intensity for nodules that have remained stable beyond this timepoint. Rather, the apparent plateau underscores the inherent limitations of pooling proportional outcome data across studies with

heterogeneous follow-up durations. Future research employing individual patient-level data with standardized follow-up intervals would be necessary to accurately characterize the true temporal trajectory of hypervascular transformation risk.

5.3.3 Nodule Size as a Predictor of Transformation

The identification of **baseline nodule size greater than 9 mm** as the only statistically significant predictor of hypervascular transformation in this meta-analysis corroborates findings from multiple individual studies discussed in the literature review. The meta-regression analysis carried out by Saitoh et al., 2018 reported that nodules greater than 10 mm demonstrated higher transformation rates than subcentimeter lesions.

The 9 mm threshold identified in this study is clinically meaningful and consistent with the operational approach commonly used in clinical practice, which distinguishes nodules smaller than 10 mm (lower risk) from those 10 mm or larger (higher risk) when determining surveillance intervals and considering biopsy (Kokudo et al., 2019). The scientific basis for this association likely reflects that bigger nodules:

- **Have undergone longer periods of growth**, allowing for accumulation of additional genetic alterations
- **May represent more advanced stages of dysplasia** with greater likelihood of having acquired the molecular changes necessary for neoangiogenesis
- **Are closer to the threshold for radiological detection** of arterial hyperenhancement

However, it is important to emphasize that even smaller nodules (<9 mm) demonstrated a considerable transformation rate of 26.8%, indicating that nodule size alone cannot exclude malignant potential.

5.3.4 Follow-Up Duration Paradox

A counterintuitive finding of this analysis was the **inverse relationship** between follow-up duration and transformation rates in subgroup analysis ($p = 0.020$). Studies with longer follow-up (>750 days) reported lower transformation rates, 19.8%, compared to short-term studies, 34.6%. This paradox is likely attributable to several methodological factors, as previously described, namely:

1. **Survivor Bias**: Nodules that transform early are removed from surveillance (via treatment or reclassification), leaving a cohort of "stable" nodules in long-term studies.
2. **Competing Risks**: Patients with cirrhosis have significant mortality from liver failure, variceal bleeding, and other complications. Those who survive long enough for extended follow-up may represent a healthier subgroup with inherently lower transformation risk.
3. **Proportional vs. Time-to-Event Outcomes**: The use of cumulative proportions rather than hazard rates obscures the temporal dynamics of transformation. Kaplan-Meier or Cox regression analyses would more accurately capture the time-dependent nature of this outcome.
4. **Denominator Attrition**: Long-term studies may lose patients to follow-up, transplantation, or death, reducing the denominator and potentially biasing the observed proportion.

This finding highlights a critical limitation of proportional outcome measures in surveillance studies and supports the use of **time-to-event analyses** in future research.

5.3.5 MRI Machine Type as a Predictor of Transformation

The meta-regression analysis for MRI machine type (1.5T vs. 1.5T/3T) yielded a non-significant p-value ($p = 0.99$), suggesting that field strength alone does not significantly influence reported transformation rates. However, as noted in the literature review, variations in imaging protocols, including specific sequences, contrast agent dosing, and timing of acquisition phases, may contribute to methodological heterogeneity that cannot be fully captured by field strength alone (Y.Y. Kim et al., 2019).

5.3.6 Implications for Clinical Management and Surveillance

The findings of this meta-analysis have direct implications for the clinical management of patients with chronic liver disease who present with hypovascular, hypointense nodules on gadoxetic acid–enhanced MRI. Current guidelines, including those from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), provide recommendations for the diagnosis and management of HCC but offer limited detailed guidance regarding the management of non-hypervascular nodules.

Based on the substantial transformation rate identified in this study, several management strategies merit consideration:

- **Enhanced Surveillance Protocols**: Considering the 19.7% transformation rate at 1 year, consideration should be given to more frequent imaging surveillance (e.g., every 3–4 months) during the first year following detection,

rather than the standard 6-month interval typically recommended for cirrhotic patients without focal lesions.

- **Risk-Stratified Management**:
    - Patients with **larger nodules (≥9 mm)** may benefit from more aggressive surveillance or consideration for early biopsy to establish a definitive diagnosis, especially when clinical suspicion of malignancy is increased due to additional risk factors such as elevated alpha-fetoprotein (AFP), rapid nodule growth, or high-risk underlying liver disease aetiology.
    - **Patients with smaller nodules (<9 mm)** may be managed with standard surveillance protocols, though continued follow-up remains important given the non-negligible transformation rate of 26.8%
- **Multidisciplinary Discussion**: Cases presenting with hypovascular hypointense nodules should be discussed in multidisciplinary meetings to integrate clinical, laboratory, and imaging data and determine the most appropriate personalised management plans.
- **Patient Counselling**: Patients should be advised of the significant risk of transformation and the importance of complying with surveillance protocols, as early detection of hypervascular transformation may facilitate curative interventions such as resection, ablation, or transplantation, which have been shown to improve long-term outcomes in early-stage HCC (Y.S. Kim et al., 2016; Pawlik et al., 2005)

5.4 Strengths and Limitations

5.4.1 Strengths

This systematic review and meta-analysis contains multiple essential characteristics which enhance the reliability and validity of its obtained results. The search method which spanned multiple databases (PubMed, Web of Science, Scopus) used a specific search string to find relevant studies while manual reference evaluation helped identify all important research findings. The study included only studies which met specific inclusion and exclusion criteria (Table 1) that required both minimum participant numbers and validated reference standards and specific imaging protocols.

The study benefits from its relatively large sample size which includes 18 studies with 1,563 patients and 2,136 nodules to achieve strong statistical power for detecting significant effects and generating precise pooled estimates. The research design used time-dependent statistical methods to evaluate the likelihood of hypervascular transformation developed over three consecutive years. The researchers conducted a thorough analysis of transformation predictors through meta-regression and subgroup analysis to identify both heterogeneity sources and essential clinical predictors. The review becomes more understandable and reproducible through PRISMA principles which document all review procedures starting from search methods to statistical evaluation.

The use of Rayyan.ai, which is a dedicated systematic review management software, further enhanced the efficiency and accuracy of the screening process. This software facilitated de-duplication of records across databases, enabled organised tracking of screening decisions, and provided an audit trail of the selection process. The use of such specialised software represents current best practice in

systematic review methodology and helps ensure that the screening process was conducted systematically and without error.

5.4.2 Limitations

5.4.2.1 Limited Number of Studies for Time-Dependent Analyses

One of the most significant limitations of this meta-analysis is the **progressively diminishing pool of studies** contributing to the time-dependent cumulative incidence rate analyses:

Table 12: Summary of Overall and 1-Year, 2-Year, and 3-Year Cumulative Incidence Rates

Time Point	Number of Studies	Pooled Estimate (95% CI)	I^2
Overall	18 studies	34.4% (28.7%–40.2%)	87.5%
1-Year	10 studies	19.7% (9.1%–30.4%)	97.5%
2-Year	6 studies	27.9% (16.3%–39.5%)	94.9%
3-Year	**4 studies**	27.2% (17.7%–36.7%)	83.1%

Implications of the Small 3-Year Study Pool

The **3-year cumulative incidence rate analysis relied on only 4 studies** (Y.S. Kim et al., 2016; Yun Ku Cho et al., 2018; Park et al., 2022; Yang et al., 2018), which introduces a number of critical concerns:

- **Reduced Statistical Power**: With only 4 studies, the analysis has limited statistical power to detect true effects and to reliably estimate the pooled proportion. The precision of the pooled estimate is inherently compromised,

as reflected in the relatively wide 95% confidence interval (17.7%–36.7%), spanning nearly 20 percentage points.

- **Vulnerability to Outlier Influence**: In small meta-analyses, a single outlier study can disproportionately influence the pooled estimate. Examination of the individual 3-year rates reveals significant variation:

    1. Y.S. Kim et al. (2016): 32.3%
    2. Yun Ku Cho et al. (2018): 39.0%
    3. Park et al. (2022): 17.5%
    4. Yang et al. (2018): 21.3%

The difference between the highest (39.0%) and lowest (17.5%) reported rates is more than two-fold, indicating substantial variability that cannot be adequately explored with only 4 studies.

5.4.2.2. Substantial Heterogeneity Across All Analyses

The meta-analysis consistently identified **significant levels of heterogeneity** across all pooled analyses, with I^2 values ranging from 83.1% to 97.5%:

Table 13: Summary of Heterogeneity Across All Pooled Analyses

Analysis	I^2 Statistic	Interpretation
Overall pooled proportion	87.5%	Considerable heterogeneity
1-Year cumulative incidence	97.5%	Considerable heterogeneity
2-Year cumulative incidence	94.9%	Considerable heterogeneity
3-Year cumulative incidence	83.1%	Considerable heterogeneity

According to the Cochrane Handbook for Systematic Reviews of Interventions, I^2 values of 75–100% represent **considerable heterogeneity**, indicating that the

majority of variability in effect size estimates is attributable to true between-study differences rather than sampling error.

Consequences of High Heterogeneity:

- **Questionable Validity of Pooled Estimates**: When heterogeneity is substantial, the pooled estimate may not represent a single "true" effect but rather an average of disparate effects that vary meaningfully across studies. The clinical utility of such an average is questionable.
- **Limited Ability to Identify Sources**: Despite meta-regression analyses, only nodule size was identified as a significant source of heterogeneity. The remaining unexplained heterogeneity suggests that important moderating factors were either not measured or not reported consistently across studies.

5.4.2.3 Reliance on Observational Study Design

Only observational study designs were included in this systematic review and meta-analysis. Observational studies include retrospective and prospective cohorts; however, these methods create three major biases that affect the results, namely **selection bias, information bias, and confounding**. Given the nature of the research question, which is based on the hypervascular transformation of hypovascular, hypointense liver nodules, the lack of randomised controlled trials is understandable because of its natural occurrence. However, this approach limits the ability to establish cause-and-effect relationships from the obtained results. In addition, this meta-analysis used study-level information instead of patient-specific data, which limited its ability to perform complex statistical models that would have controlled confounding factors more effectively.

5.4.2.4 Heterogeneity in Imaging Protocols and Technology

Despite the meta-regression analysis showing no significant effect of MRI field strength (1.5T vs. 1.5T/3T; p-value = 0.99), substantial **methodological heterogeneity in imaging protocols** likely contributed to the observed variability:

- **MRI Sequences and Parameters**: Studies varied in the specific sequences used (e.g., T1-weighted, T2-weighted, diffusion-weighted imaging), sequence parameters (e.g., echo time, repetition time, flip angle), and acquisition techniques (e.g., breath-hold vs. respiratory-triggered).
- **Contrast Agent Dosing**: While all studies used gadoxetic acid, variations in dosing protocols (e.g., weight-based vs. fixed dose, injection rate) may affect the degree of hepatocyte uptake and signal intensity on HBP imaging.
- **Timing of Hepatobiliary Phase Acquisition**: The HBP is typically acquired 15–20 minutes post-injection, but variations in timing across studies may affect the degree of contrast uptake and the conspicuity of hypointense nodules.
- **Image Interpretation**: Inter-reader and intra-reader variability in image interpretation may affect the identification and characterization of HHNs, even when using standardized criteria.

5.4.2.5 Geographic and Demographic Limitations

As the majority of studies included in this analysis were carried out in Asian countries (Japan, Korea, and China), where hepatitis B is more prevalent, this may create doubts about the generalisability of these findings to Western populations with different aetiologies of liver disease, including hepatitis C, alcoholic liver disease, and non-alcoholic fatty liver disease. Furthermore, differences in access to healthcare, surveillance practices, and treatment approaches across different healthcare systems may affect the detection and management of HHNs.

5.5 Future Considerations

The findings of this meta-analysis, when combined with the identified limitations, highlight several important directions for future research. Large, prospective, multicenter studies with standardized imaging protocols, uniform diagnostic criteria, and systematic follow-up procedures are needed to provide more reliable estimates of transformation rates and reduce the significant heterogeneity observed in this analysis. Collaboration among research groups to pool individual patient-level data would allow for more sophisticated analytical approaches, such as multivariable regression models, which better control for confounding and identify patient-specific risk factors with greater precision.

The integration of molecular and genetic biomarkers (such as circulating tumour DNA, genetic risk scores, and serum biomarkers) with conventional imaging characteristics shows a promising approach to improving risk stratification and prediction of malignant transformation. Similarly, investigation of advanced MRI techniques, including diffusion-weighted imaging, perfusion imaging, and radiomics-based approaches, may enhance the characterization of hypovascular nodules and provide earlier detection of features predictive of transformation.

From a health economics perspective, thorough cost-effectiveness analyses comparing different surveillance strategies, such as varying frequencies of imaging and the incorporation of additional biomarkers, are essential to inform resource allocation decisions and the development of evidence-based clinical guidelines. Most significantly, the best level of evidence to support management choices would come from randomized controlled trials comparing the clinical effects of early intervention, such as ablation of high-risk nodules, with ongoing surveillance.

Patient-centered outcomes, such as overall survival, quality of life, and complication rates, would need to be measured in such trials.

Lastly, individualized risk assessment and customized management plans based on each patient's specific risk profile would be made possible by the creation and external validation of thorough clinical risk prediction models that incorporate a variety of variables, such as nodule size, patient demographics, underlying liver disease characteristics, and biomarkers. These models should be validated across diverse populations and geographic regions to ensure broad applicability and generalizability.

5.6 Conclusion

In conclusion, this meta-analysis of 18 studies, including 2,136 hypovascular hepatic nodules, demonstrates that approximately one-third of these HHN nodules (**34.4%**) undergo hypervascular transformation during MRI surveillance. **Mean initial nodule size** is the most significant predictor of transformation, with nodules ≥9 mm having a 35.3% transformation rate compared to 26.8% for smaller nodules ($p = 0.0035$). Patient age, MRI field strength, and follow-up duration do not independently predict transformation after adjustment.

These findings support **size-based risk stratification** in the surveillance of hypovascular hepatic nodules detected on gadoxetic acid-enhanced MRI. Clinicians should consider intensified surveillance or earlier intervention for nodules approaching or exceeding 9–10 mm. The substantial residual heterogeneity (76.8%) indicates that additional factors influence transformation risk, highlighting the need for individualized assessment and future research incorporating patient-level data and time-to-event analyses.

Bibliography

Aubé, C., Oberti, F., Lonjon, J., Pageaux, G., Seror, O., N'Kontchou, G., Rode, A., Radenne, S., Cassinotto, C., Vergniol, J., Bricault, I., Leroy, V., Ronot, M., Castera, L., Michalak, S., Esvan, M., Vilgrain, V., & CHIC Group (2017). EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. Liver international : official journal of the International Association for the Study of the Liver, 37(10), 1515–1525. https://doi.org/10.1111/liv.13429

Briani, C., Di Pietropaolo, M., Marignani, M., Carbonetti, F., Begini, P., David, V., & Iannicelli, E. (2018). Non-Hypervascular Hypointense Nodules at Gadoxetic Acid MRI: Hepatocellular Carcinoma Risk Assessment with Emphasis on the Role of Diffusion-Weighted Imaging. Journal of gastrointestinal cancer, 49(3), 302–310. https://doi.org/10.1007/s12029-017-9952-7

Campani, C., Zucman-Rossi, J., & Nault, J. C. (2023). Genetics of Hepatocellular Carcinoma: From Tumor to Circulating DNA. *Cancers*, *15*(3), 817. https://doi.org/10.3390/cancers15030817

Chen, C. J., Yang, H. I., Su, J., Jen, C. L., You, S. L., Lu, S. N., Huang, G. T., Iloeje, U. H., & REVEAL-HBV Study Group (2006). Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA, 295(1), 65–73. https://doi.org/10.1001/jama.295.1.65

Di Pietropaolo, M., Briani, C., Federici, G. F., Marignani, M., Begini, P., Delle Fave, G., & Iannicelli, E. (2015). Comparison of diffusion-weighted imaging and gadoxetic acid-enhanced MR images in the evaluation of hepatocellular carcinoma and hypovascular hepatocellular nodules. Clinical imaging, 39(3), 468–475. https://doi.org/10.1016/j.clinimag.2014.12.020

El-Serag, H. B., & Marrero, J. A. (2020). Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology, 158(6), 1499–1514.

Hectors, S. J., Wagner, M., Besa, C., Huang, W., & Taouli, B. (2018). Multiparametric FDG-PET/MRI of Hepatocellular Carcinoma: Initial Experience. *Contrast media & molecular imaging*, *2018*, 5638283. https://doi.org/10.1155/2018/5638283

Hyodo, T., Murakami, T., Imai, Y., Okada, M., Hori, M., Kagawa, Y., Kogita, S., Kumano, S., Kudo, M., & Mochizuki, T. (2013). Hypovascular nodules in patients with chronic liver disease: risk factors for development of hypervascular hepatocellular carcinoma. Radiology, 266(2), 480–490. https://doi.org/10.1148/radiol.12112677

Iannicelli, E., Di Pietropaolo, M., Marignani, M., Briani, C., Federici, G. F., Delle Fave, G., & David, V. (2014). Gadoxetic acid-enhanced MRI for hepatocellular carcinoma and hypointense nodule observed in the hepatobiliary phase. La Radiologia medica, 119(6), 367–376. https://doi.org/10.1007/s11547-013-0364-x

Inoue, T., Hyodo, T., Murakami, T., Takayama, Y., Nishie, A., Higaki, A., Korenaga, K., Sakamoto, A., Osaki, Y., Aikata, H., Chayama, K., Suda, T., Takano, T., Miyoshi, K., Koda, M., Numata, K., Tanaka, H., Iijima, H., Ochi, H., Hirooka, M., … Kudo, M. (2013). Hypovascular hepatic nodules showing hypointense on the hepatobiliary-phase image of Gd-EOB-DTPA-enhanced MRI to develop a hypervascular hepatocellular carcinoma: a nationwide retrospective study on their natural course and risk factors. Digestive diseases (Basel, Switzerland), 31(5-6), 472–479. https://doi.org/10.1159/000355248

International Consensus Group for Hepatocellular NeoplasiaThe International Consensus Group for Hepatocellular Neoplasia (2009). Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology (Baltimore, Md.), 49(2), 658–664. https://doi.org/10.1002/hep.22709

Joo, I., & Lee, J. M. (2016). Recent Advances in the Imaging Diagnosis of Hepatocellular Carcinoma: Value of Gadoxetic Acid-Enhanced MRI. *Liver cancer*, *5*(1), 67–87. https://doi.org/10.1159/000367750

Kanefuji, T., Takano, T., Suda, T., Akazawa, K., Yokoo, T., Kamimura, H., Kamimura, K., Tsuchiya, A., Takamura, M., Kawai, H., Yamagiwa, S., Aoyama, H., Nomoto, M., & Terai, S. (2015). Factors predicting aggressiveness of non-hypervascular hepatic nodules detected on hepatobiliary phase of gadolinium ethoxybenzyl diethylene-triamine-pentaacetic-acid magnetic resonance imaging. *World journal of gastroenterology*, *21*(15), 4583–4591. https://doi.org/10.3748/wjg.v21.i15.4583

Kim, Y. K., Lee, W. J., Park, M. J., Kim, S. H., Rhim, H., & Choi, D. (2012). Hypovascular hypointense nodules on hepatobiliary phase gadoxetic acid-enhanced MR images in patients with cirrhosis: potential of DW imaging in predicting progression to hypervascular HCC. *Radiology*, *265*(1), 104–114. https://doi.org/10.1148/radiol.12112649

Kim, Y. S., Song, J. S., Lee, H. K., & Han, Y. M. (2016). Hypovascular hypointense nodules on hepatobiliary phase without T2 hyperintensity on gadoxetic acid-enhanced MR images in patients with chronic liver disease: long-term outcomes and risk factors for hypervascular transformation. *European radiology*, *26*(10), 3728–3736. https://doi.org/10.1007/s00330-015-4146-9

Kim, Y. Y., Park, M. S., Aljoqiman, K. S., Choi, J. Y., & Kim, M. J. (2019). Gadoxetic acid-enhanced magnetic resonance imaging: Hepatocellular carcinoma and mimickers. *Clinical and molecular hepatology*, *25*(3), 223–233. https://doi.org/10.3350/cmh.2018.0107

Koh, D. M., Collins, D. J., & Orton, M. R. (2015). Intravoxel incoherent motion in body diffusion-weighted MRI: Reality and challenges. American Journal of Roentgenology, 196(6), 1351–1361.

Kokudo, N., Takemura, N., Hasegawa, K., Takayama, T., Kubo, S., Shimada, M., Nagano, H., Hatano, E., Izumi, N., Kaneko, S., Kudo, M., Iijima, H., Genda, T., Tateishi, R., Torimura, T., Igaki, H., Kobayashi, S., Sakurai, H., Murakami, T., Watadani, T., … Matsuyama, Y. (2019). Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatology research : the official journal of the Japan Society of Hepatology*, *49*(10), 1109–1113. https://doi.org/10.1111/hepr.13411

Lee, D. H., Lee, J. M., Lee, J. Y., Kim, S. H., Kim, J. H., Yoon, J. H., Kim, Y. J., Lee, J. H., Yu, S. J., Han, J. K., & Choi, B. I. (2015). Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. *Journal of hepatology*, *62*(5), 1122–1130. https://doi.org/10.1016/j.jhep.2014.12.015

Liu, Z., Wang, S., Dong, D., Wei, J., Fang, C., Zhou, X., Sun, K., Li, L., Li, B., Wang, M., & Tian, J. (2019). The Applications of Radiomics in Precision Diagnosis and Treatment of Oncology: Opportunities and Challenges. *Theranostics*, *9*(5), 1303–1322. https://doi.org/10.7150/thno.30309

Llovet, J. M., Montal, R., Sia, D., & Finn, R. S. (2018). Molecular therapies and precision medicine for hepatocellular carcinoma. *Nature reviews. Clinical oncology*, *15*(10), 599–616. https://doi.org/10.1038/s41571-018-0073-4

Marrero, J. A., Kulik, L. M., Sirlin, C. B., Zhu, A. X., Finn, R. S., Abecassis, M. M., Roberts, L. R., & Heimbach, J. K. (2018). Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md.), 68(2), 723–750. https://doi.org/10.1002/hep.29913

Matsui, O., Kadoya, M., Kameyama, T., Yoshikawa, J., Takashima, T., Nakanuma, Y., Unoura, M., Kobayashi, K., Izumi, R., & Ida, M. (1991). Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. *Radiology*, *178*(2), 493–497. https://doi.org/10.1148/radiology.178.2.1846240

Motosugi, U., Ichikawa, T., Sou, H., Sano, K., Tominaga, L., Muhi, A., & Araki, T. (2010). Distinguishing hypervascular pseudolesions of the liver from hypervascular hepatocellular carcinomas with gadoxetic acid-enhanced MR imaging. *Radiology*, *256*(1), 151–158. https://doi.org/10.1148/radiol.10091885

Ozaki, K., Tanahashi, Y., & Goshima, S. (2025). Gadoxetic acid-enhanced MRI in hepatocellular carcinoma: A comprehensive review of diagnostic, surveillance, and treatment response prediction and assessment. *Japanese Journal of Radiology*. https://doi.org/10.1007/s11604-025-01870-x

Park, H. J., Lee, T. Y., Kim, S. Y., Kim, M. J., Singal, A. G., Lee, S. J., Won, H. J., Byun, J. H., & Lim, Y. S. (2022). Hypervascular transformation of hepatobiliary phase hypointense nodules without arterial phase hyperenhancement on gadoxetic acid-enhanced MRI: long-term follow-up in a surveillance cohort. *European radiology*, *32*(8), 5064–5074. https://doi.org/10.1007/s00330-022-08623-8

Park Y. N. (2011). Update on precursor and early lesions of hepatocellular carcinomas. *Archives of pathology & laboratory medicine*, *135*(6), 704–715. https://doi.org/10.5858/2010-0524-RA.1

Pawlik, T. M., Abdalla, E. K., Ellis, L. M., Vauthey, J. N., & Curley, S. A. (2006). Debunking dogma: surgery for four or more colorectal liver metastases is justified. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*, *10*(2), 240–248. https://doi.org/10.1016/j.gassur.2005.07.027

Rosenkrantz, A. B., Pinnamaneni, N., Kierans, A. S., & Ream, J. M. (2016). Hypovascular hepatic nodules at gadoxetic acid-enhanced MRI: whole-lesion hepatobiliary phase histogram metrics for prediction of progression to arterial-enhancing hepatocellular carcinoma. *Abdominal radiology (New York)*, *41*(1), 63–70. https://doi.org/10.1007/s00261-015-0610-x

Saitoh, T., Sato, S., Yazaki, T., Tobita, H., Miyake, T., Ishihara, S., Katsube, T., Kitagaki, H., & Kinoshita, Y. (2018). Progression of Hepatic Hypovascular Nodules with Hypointensity in the Hepatobiliary Phase of Gd-EOB-DTPA-enhanced MRI in Hepatocellular Carcinoma Cases. *Internal medicine (Tokyo, Japan)*, *57*(2), 165–171. https://doi.org/10.2169/internalmedicine.8801-16

Sasaki, K., Shindoh, J., Margonis, G. A., Nishioka, Y., Andreatos, N., Sekine, A., Hashimoto, M., & Pawlik, T. M. (2017). Effect of Background Liver Cirrhosis on Outcomes of Hepatectomy for Hepatocellular Carcinoma. *JAMA surgery*, *152*(3), e165059. https://doi.org/10.1001/jamasurg.2016.5059

Suh, C. H., Kim, K. W., Pyo, J., Lee, J., Kim, S. Y., & Park, S. H. (2017). Hypervascular Transformation of Hypovascular Hypointense Nodules in the Hepatobiliary Phase of Gadoxetic Acid-Enhanced MRI: A Systematic Review and Meta-Analysis. AJR. American journal of roentgenology, 209(4), 781–789. https://doi.org/10.2214/AJR.16.17711

Takara, K., Saito, K., Saguchi, T., Sugimoto, K., Taira, J., Imai, Y., Moriyasu, F., Akata, S., & Tokuuye, K. (2014). Is diffusion-weighted imaging a significant indicator of the development of vascularization in hypovascular hepatocellular lesions?. *Clinical imaging*, *38*(4), 458–463. https://doi.org/10.1016/j.clinimag.2014.03.013

Takayama, Y., Nishie, A., Nakayama, T., Asayama, Y., Ishigami, K., Kakihara, D., Ushijima, Y., Fujita, N., Hirakawa, M., & Honda, H. (2012). Hypovascular hepatic nodule showing hypointensity in the hepatobiliary phase of gadoxetic acid-enhanced MRI in patients with chronic liver disease: prediction of malignant transformation. *European journal of radiology*, *81*(11), 3072–3078. https://doi.org/10.1016/j.ejrad.2012.05.008

Takechi, M., Tsuda, T., Yoshioka, S., Murata, S., Tanaka, H., Hirooka, M., & Mochizuki, T. (2012). Risk of hypervascularization in small hypovascular hepatic nodules showing hypointense in the hepatobiliary phase of gadoxetic acid-enhanced MRI in patients with chronic liver disease. *Japanese journal of radiology*, *30*(9), 743–751. https://doi.org/10.1007/s11604-012-0120-5

Tang, J. C., Feng, Y. L., Guo, T., Xie, A. Y., & Cai, X. J. (2016). Circulating tumor DNA in hepatocellular carcinoma: trends and challenges. Cell & bioscience, 6, 32. https://doi.org/10.1186/s13578-016-0100-z

Teerasamit, W., Hongpinyo, S. ., Tongdee, R. ., & Suvannarerg, V. . (2023). Predicting Progression to Hypervascular HCC in Hypovascular Hypointense Nodules in Gadoxetic Acid-enhanced MR Images in Patients with Chronic Liver Disease. Siriraj Medical Journal, 75(9), 680–687. https://doi.org/10.33192/smj.v75i9.262021

Wang, F., Numata, K., Chuma, M., Nihonmatsu, H., Moriya, S., Nozaki, A., Ogushi, K., Fukuda, H., Okada, M., Ruan, L., Luo, W., Koizumi, N., Nakano, M., Otani, M., Inayama, Y., & Maeda, S. (2021). The value of hepatobiliary phase in EOB-MRI in predicting hypervascularization outcome of non-hypervascular hypointense lesions in high-risk patients for hepatocellular carcinoma. *Abdominal radiology (New York)*, *46*(6), 2527–2539. https://doi.org/10.1007/s00261-020-02881-0

Yang, H. J., Song, J. S., Choi, E. J., Choi, H., Yang, J. D., & Moon, W. S. (2018). Hypovascular hypointense nodules in hepatobiliary phase without T2 hyperintensity: long-term outcomes and added value of DWI in predicting hypervascular transformation. *Clinical imaging*, *50*, 123–129. https://doi.org/10.1016/j.clinimag.2018.01.003

Yun Ku Cho, E., & Kim, M. Y. (2018). Long-term outcome of hypointense nodules on hepatobiliary phase gadoxetic acid-enhanced MRI. Korean Journal of Radiology, 19(5), 903–912.

Zucman-Rossi, J., Villanueva, A., Nault, J. C., & Llovet, J. M. (2015). Genetic Landscape and Biomarkers of Hepatocellular Carcinoma. *Gastroenterology*, *149*(5), 1226–1239.e4. https://doi.org/10.1053/j.gastro.2015.05.061