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Research Article

Prevalence of Atypical Hepatocellular Carcinoma in Advanced Chronic Liver Disease Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Hepatocellular Carcinoma (HCC) is the most prevalent primary liver cancer, typically developing in chronic liver disease, particularly cirrhosis. Early detection is crucial for improving patient outcomes, with imaging serving as the primary method. However, the presence of atypical HCC, which deviates from the typical radiological, pathological, or clinical presentation of classical HCC, poses diagnostic challenges. This systematic review and meta-analysis aimed to assess the prevalence of atypical HCC in patients with Advanced Chronic Liver Disease (ACLD) and discuss its diagnostic challenges and clinical implications. Methods: The study followed PRISMA guidelines and included 13 studies with a total of 1088 atypical HCC nodules.

Results: The random-effects model yielded a pooled effect size of 0.368 (95% CI: 0.248, 0.489), indicating a moderate prevalence of atypical HCC nodules in ACLD patients. Subgroup analysis and sensitivity analysis were performed to address heterogeneity and outliers. The final pooled effect size was 0.36 (95% CI: 0.2309, 0.4971) after excluding outliers, with moderate heterogeneity (I^2 = 78.74%).

Conclusion: The findings suggest that current diagnostic algorithms relying solely on typical contrast enhancement patterns may fail to identify up to one-third of HCC cases presenting atypically. Recommendations include implementing standardized reporting protocols, developing more sophisticated diagnostic algorithms incorporating multiple imaging tools and biochemical parameters, and increasing awareness among radiologists and hepatologists. Future research should aim for larger sample sizes, implement standardized reporting protocols, and incorporate meta-regression to examine factors contributing to effect size variation. The limitations of the meta-analysis include high remaining heterogeneity, potential small-study effects, and the possibility of unmeasured confounders.

Keywords: Atypical hepatocellular carcinoma, Typical hepatocellular carcinoma, Triple phase enhanced CT, Triple phase enhanced MRI

Introduction

Hepatocellular Carcinoma (HCC) is the most prevalent type of primary liver cancer. It typically develops in chronic liver disease, particularly in cirrhosis. HCC is characterized by its aggressive nature and poor prognosis when diagnosed at an advanced stage [1]. It is the fifth leading cause of cancer worldwide and the second leading cause of cancer-related mortality in males [2]. Early detection and intervention are critical to improve patient outcomes [3]. Imaging serves as the primary method for early detection of

HCC and exhibits a characteristic appearance on triple-phase contrast-enhanced CT and MRI. However, numerous challenges persist in diagnosis, despite advancements in scanning techniques and contrast media. These challenges primarily stem from the presence of atypical HCC, which refers to liver tumours that deviate from the typical radiological, pathological, or clinical presentation of classical HCC, as well as variants of HCC, such as fibrolamellar and sarcomatoid types, which also present diagnostic difficulties owing to their unusual features [4]. Atypical HCCs not only pose greater diagnostic challenges but also have implications for management and differentiation from other benign liver lesions such as focal nodular hyperplasia, atypical hemangioma, and cholangiocarcinoma [5]. There is also a need to enhance the planning of diagnostic and management strategies [6-8], and it is prudent to first determine the extent of this issue [8,9]. Consequently, it is necessary to conduct a systematic review and meta-analysis of this problem to investigate its prevalence in patients with ACLD and discuss its implications.

Objective of the Systematic Review and Meta-Analysis

a) To comprehensively assess and synthesize available evidence on the occurrence of atypical HCC in patients with ACLD with the aim of providing a more precise estimate of its prevalence.

b) To identify potential diagnostic challenges and clinical implications associated with atypical HCC in the context of ACLD based on the findings of this review, which would not only address potential knowledge gaps but also enhance surveillance strategies and inform future clinical practices [8-20].

Methods

The present study was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and published guidelines. No ethics permission or consent was required because the study involved only a systematic review of the literature and synthesis of the existing data.

Search Strategy

The search strategy involved the retrieval of eligible studies of Atypical HCC nodules, which included a search of electronic databases such as PubMed, MEDLINE, Google Scholar, Sci space, and Mendeley. Relevant keywords and Medical Subject Heading (MeSH) terms related to atypical HCC, ACLD, atypical presentations of HCC, triple-phase CECT, and MRI were used for the initial search, in both isolated and combined manners. The specific data range was set from 2001 to 2024 for 24 years. Cross-references of the articles will also be reviewed, and a listing prepared. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) statement model of the systematic review workflow was subsequently used to screen the articles and determine their eligibility for the study. All shortlisted articles were determined for full data availability and relevance to the context of the review study. The final articles were evaluated according to the inclusion criteria and were enrolled.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

a) All studies should have a minimum of 70 patients of ACLD

b) The study should include at least 25 atypical HCC nodules or patients.

c) Studies should have an adult population with an age group 40-80 years

d) All the patients with HCC underwent histopathological confirmation.

e) Evaluation should have been performed with triple-phase CECT, triple-phase MRI, or both.

f) Proper statistical analysis should be performed in all studies.

The Exclusion criteria were as follows:

a) Studies with no full texts were excluded.

b) All studies excluded patients who had previously received treatment.

c) Observational studies, pictorial essays with imaging features.

Data Extraction

Two investigators (AK and GM) independently reviewed the titles and abstracts of all identified studies using the previously described search criteria to identify studies that met the inclusion criteria. Each study met the requirements of the first-round inclusion criteria and underwent a full-text independent review by both reviewers. Disagreements regarding inclusion between reviewers were resolved by two clinical reviewers (JS, BS). The two reviewers (AK, GM) independently extracted the following data from each study that met the following inclusion criteria: author name, year of study, type of study, patient demographics including age, sex, nodule size, total number of patients, number of both atypical HCC and total nodules, imaging features for atypical and typical HCC nodules, presence of other lesions if any were extracted along with aetiology of ACLD and histological confirmation.

Quality assessment of the included studies was performed by two authors using the JBI analytic cross-sectional study tool, and studies with a high-quality score were considered.

Statistical Analysis

This was performed using Jamovi software for the meta-analysis of proportions. Random and fixed model effects were used, and forest plots were compared. In the case of high heterogeneity, a random model is selected owing to balanced weighting and high precision. Analysis for bias was performed using funnel plots, followed by Egger's and Begg's Mazumdar tests.

Further analysis for heterogeneity and publication bias will be performed using subgroup and sensitivity analyses and other relevant tests, depending upon the results.

Results

The initial review was conducted using PubMed, Google Scholar, Scispace, and Mendley, following the PRISMA guidelines (Figure 1). From a total of 46,213 publications, 13 met the selection criteria and were deemed appropriate for the study. The JBI quality assessment was performed for all selected papers, as presented in Table 1. Based on these six parameters, all studies demonstrated high standards, with confounding factors observed in a few studies, as shown in the table. However, these factors did not significantly diminish the overall quality of the included studies. The metadata of these studies are presented in Table 1. The studies were distributed evenly from 2002 to 2023, with a proportion being prospective and the remainder being retrospective. A total of 6110 nodules were analyzed, of which 1088 were classified as atypical HCC nodules and 4997 were typical HCC nodules. The details of these studies are presented in Table 1.

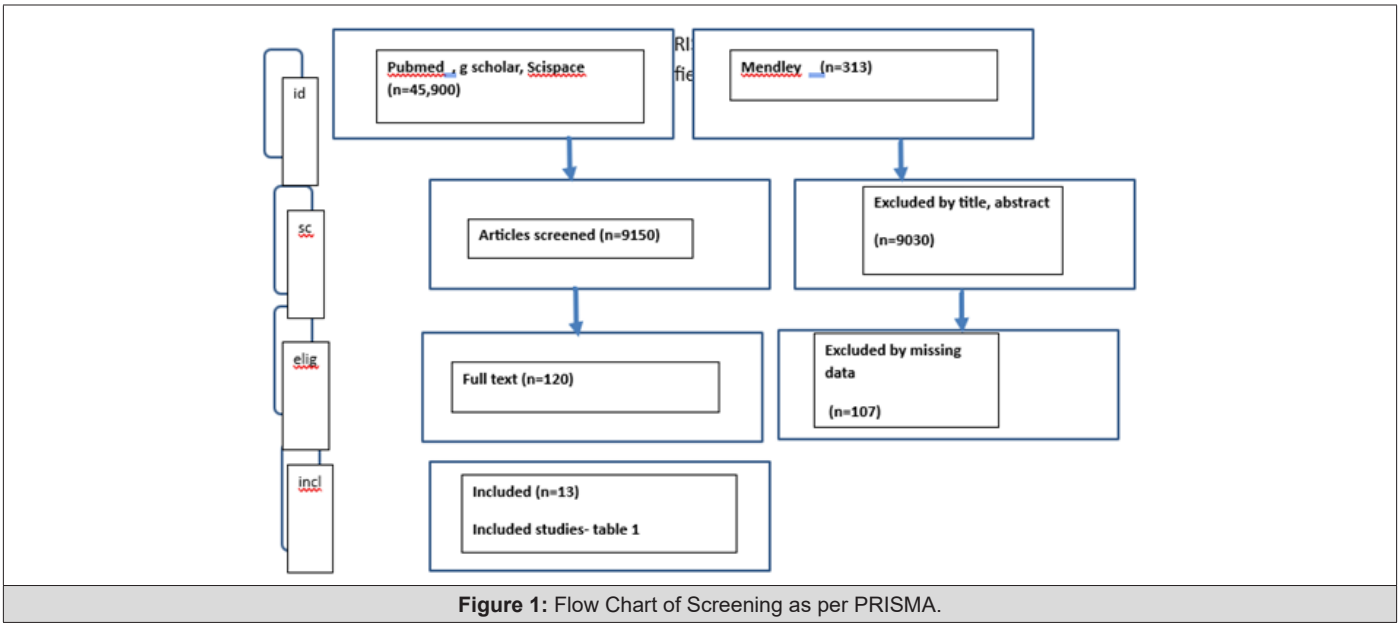

Figure 1: Flow Chart of Screening as per PRISMA.

Table 1: Study Characteristics of the selected studies for the meta-analysis.

Sno.	Author Name	Year	Type of Study	Total Patients/ Nodules	Diagnosis	Screening	Size of nodule	HCC	Atypical HCC	Non HCC	HPE	Triple Phase Features Of AHCC		
												Arterial/ hypo	Abs. wash out	Other
1	*Basha, et al.* [8]	2018	Prospective	240	ACLD	USG	<5CM	52	77	88	yes	25	10	
2	*Choi, et al.* [9]	2012	Retrospective	114	ACLD	Clinical	<3 CM	133	23		yes	16	14	
3	*Chou, et al.* [10]	2014	Prospective	75	ACLD	USG	>1.5CM	14	65		yes	13	52	
4	*Yan, et al.* [11]	2002	Prospective	71	ACLD	Clinical	<3CM	60	32		yes	22	10	
5	*Han, et al.* [12]	2023	Retrospective	129	Hep B	TPCT-MR	<3CM	53	76		yes	53	23	targetoid
6	*Huang,et al.* [13]	2016	Prospective	129	ACLD	TPCT-MR	X	488	86		yes	23	63	

7	*Ronot, et al.* [14]	2018	Retro-spec-tive	595	ACLD	TPCT-MR	X	294	47	254	yes	18	29	
8	*Kim, et al.* [15]	2015	Retro-spec-tive	376	ACLD	TPCT-MR	<5CM	294	82		yes	56	26	targe-toid
9	*Laroi, et al.* [16]	2020	Retro-spec-tive	3218	ACLD	TPCT-MR	<5CM	2916	68	234	yes	68	0	
10	*Oestman, et al.* [17]	2021	Retro-spec-tive	150	Hep B	TPCT-MR	<5CM	49	44	57	yes	14	30	
11	*Park, et al.* [18]	2021	Retro-spec-tive	1016	Hep B	TPCT-MR	<5CM	556	415	145	yes	48	230	
12	*Shin, et al.* [19]	2017	Retro-spec-tive	96	ACLD	TPCT-MR	<3CM	43	53		yes	32	11	
13	*Yoon, et al.* [20]	2018	Pro-spec-tive	130	Hep B	TPCT-MR	<3CM	45	20	65	yes	56	9	

A forest plot of the meta-analysis for the effect size of the proportion of atypical HCC nodules using random and fixed models was conducted. The Random Effects Model (Figure 2) yielded a pooled Overall Effect (95% CI) of 0.368 (0.248, 0.489), with between-study heterogeneity (τ^2) of 0.0479, I^2 (percentage of variation due to heterogeneity) of 99.3%, 95% Prediction Interval of (-0.132, 0.869), and Q-statistic of 15.01 (p = 0.2408). The study weights were relatively balanced (approximately 7.4-7.9% per study), and both models demonstrated a high I^2 of 93%; consequently, the random model was selected, with the forest plot presented in Figure 1. The fixed effects model produced a pooled Effect Size (95% CI) of 0.049 (0.044, 0.054), P-value: 0.000,0, but was substantially influenced by larger studies (particularly Study 9 with 88.3% weight) (Figure 3); therefore, a random model was chosen for subsequent analysis. These studies are listed in Table 2. The high I^2 value of 99.3% indicates that the variation between studies is not attributable solely to chance, but reflects genuine differences in study populations or methodologies, necessitating further investigation.

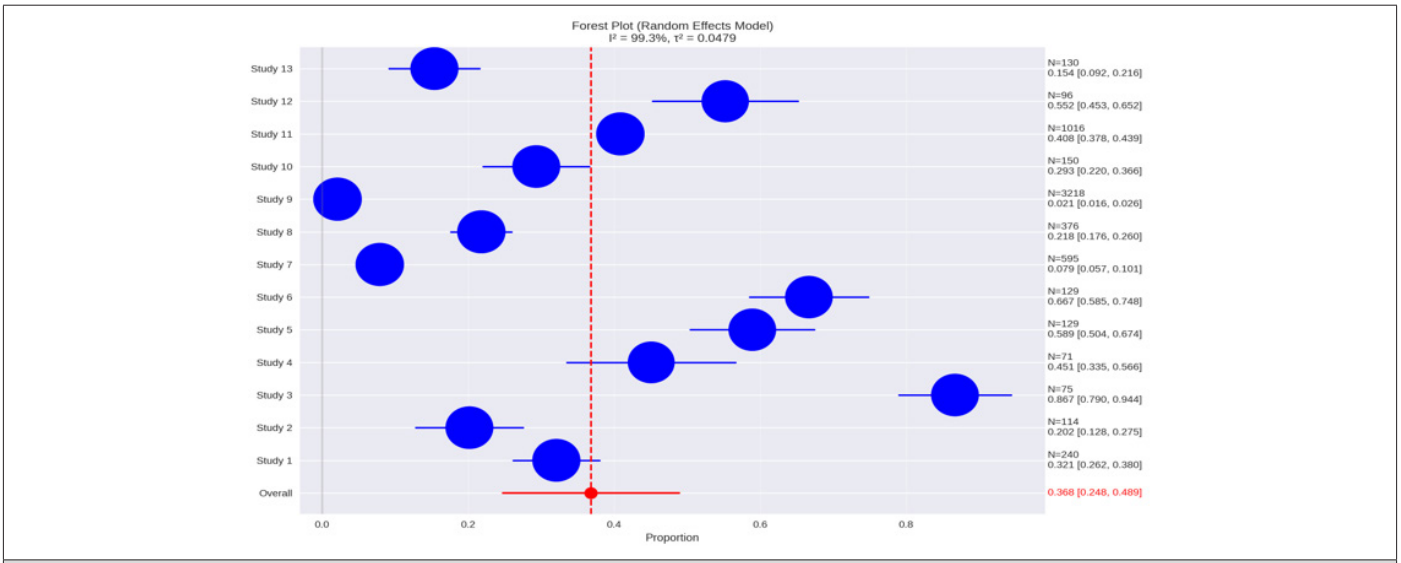

Figure 2: Forest Plot for pooled effect size of proportions for atypical HCC.

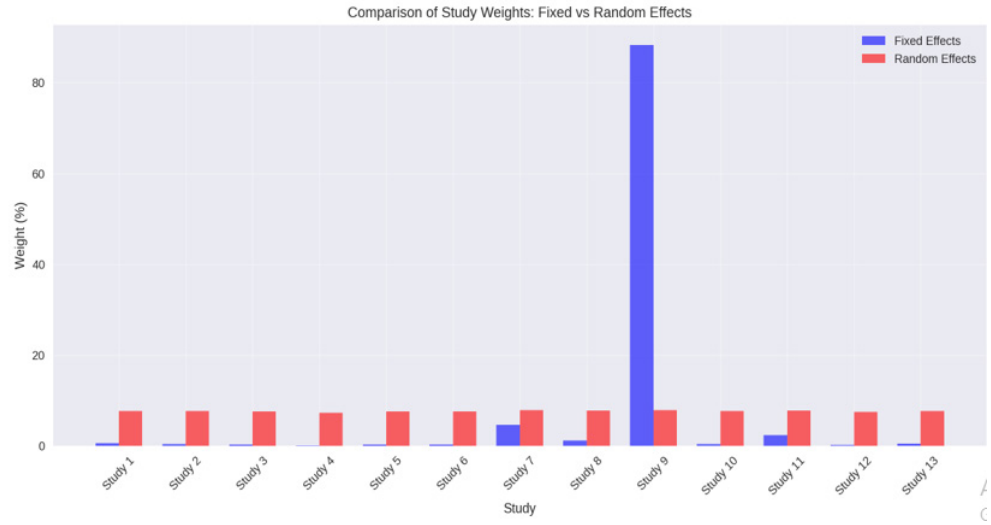

Figure 3: Comparison of study weights Fixed with Random effects size model.

Table 2: Showing subgroup analysis and leave out analysis of results on effect size.

Subgroup Analysis Results					
	Size Group	**Pooled Proportion**	**Standard Error**	**CI Lower**	**CI Upper**
0	Small	0.556339881	0.017830619	0.521391867	0.591287894
1	Medium	0.212453191	0.024096287	0.165224469	0.259681913
2	Large	0.037867231	0.002416387	0.033131112	0.042603349

Note*: Leave-One-Out Sensitivity Analysis.

Most influential studies (based on the relative change in the pooled proportion)			
	Excluded Study	**Pooled Proportion**	**Relative Change**
10	*Park, et al.* [18]	0.040037449	82.34426912
2	*Chou, et al.* [10]	0.045808353	79.79941327
7	*Kim, et al.* [15]	0.046687479	79.41173573
5	*Huang, et al.* [13]	0.046790175	79.36644885
0	*Basha, et al.* [8]	0.047121546	79.22032087

Note*: Leave-One-Out Analysis Summary.

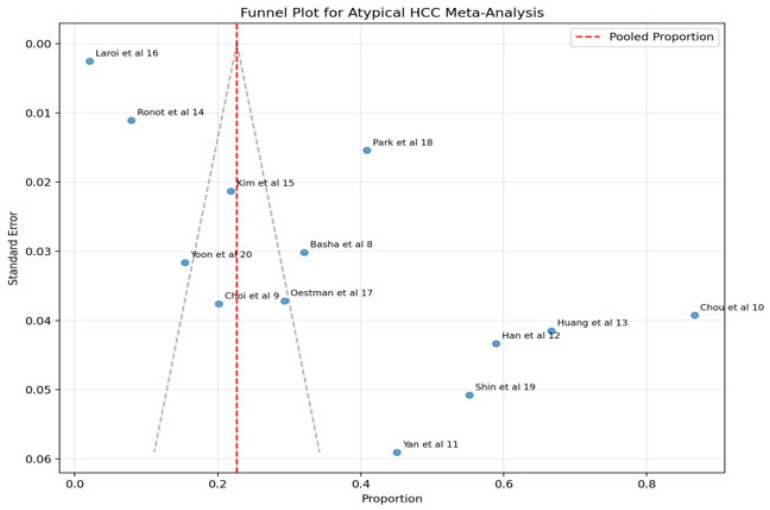

Figure 4: Funnel plot analysis for atypical HCC meta-analysis for bias assessment.

The funnel plot test was done for bias assessment (Figure 4) and showed mild asymmetry suggesting bias The funnel plot visualization exhibited asymmetry, with studies distributed unevenly around the pooled estimate (dashed red line). This asymmetry, in conjunction with the statistical tests, indicates the potential presence of publication bias in the literature. Studies with larger sample sizes (and consequently, smaller standard errors) cluster more closely around the pooled estimate, whereas studies with smaller sample sizes demonstrate greater variation and tend to report more extreme effects. Analysis of the funnel plot yielded several significant findings:

Heterogeneity Analysis: Q statistic

7418.51, Degrees of freedom: 12 and I^2 statistic: 99.8%. The exceptionally high I^2 value (99.8%) further corroborated the substantial heterogeneity between studies. b) Funnel Plot Asymmetry Test revealed a slope of -0.2347, intercept of 12.1382 (P-value = 0.0000), and R-squared = 0.9324, suggesting the presence of publication bias or small-study effects, indicating that the studies were not uniformly distributed around the mean effect size, with greater dispersion on one side.

Egger's Regression Test for Publication Bias: demonstrated an Intercept: 12.138, Slope: -0.008. The p-value for the intercept was 0.0002, which also indicated a statistically significant publication bias ($p<0.05$). Comparable results were obtained through Begg's and Mazumdar's tests, with a correlation coefficient of 0.736 (P = 0.0041), indicating a systematic bias in the study distribution.

Significant Publication Bias: It was detected by multiple methods (Egger's test and Begg's test) with high heterogeneity (τ^2 = 0.0479) and substantial variation in study sizes (ratio 45.3:1), but moderate correlation with effect sizes was effectively mitigated by the random effects model through 1. Diminishing the influence of larger studies 2. Providing balanced weight distribution 3. Accounting for between-study variance 4. Producing more conservative estimates.

Subgroup Analysis

By study and leave-out sensitivity based on study size were conducted to identify potential sources of heterogeneity and revealed that smaller studies tend to report larger effect sizes (proportions) compared to larger studies, which is a potential indicator of publication bias. Five studies identified the highest relative change (Table 3 and Figure 5)

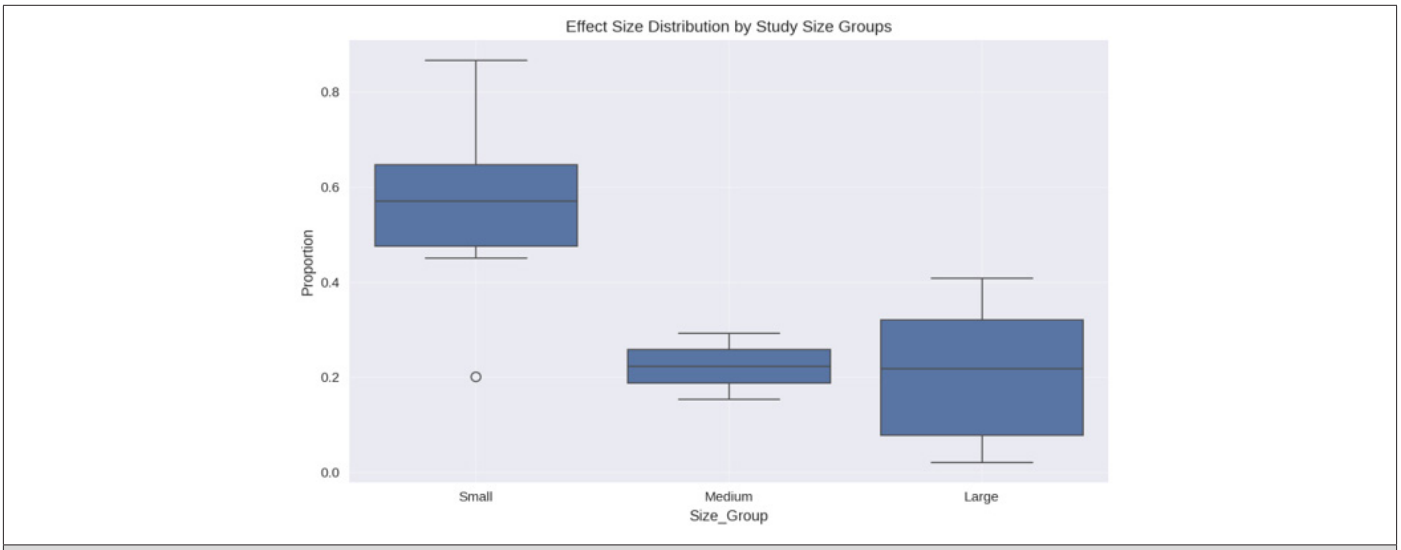

Figure 5: Box plot of Effect size distribution by study groups.

Table 3: Chart showing metadata of selected studies.

Sno.	Studies No.	Total Patients	Proportion	Std residual
1	2	114	0.202	-4.847
2	5	129	0.589	4,737
3	6	129	0.667	6.812
4	8	376	0.218	-7.788
5	12	96	0.552	3.313
6	13	130	0.154	-7.271

Study 9 contributed overwhelmingly to heterogeneity (94.6%), likely due to its large sample size and strong positive correlation (0.953) between study size and heterogeneity contribution. One potential outlier (Study 3) was identified with a Z-score > 2.

Larger studies (Size Group: Large) dominated the heterogeneity (98.37%), while smaller studies showed more variability in effect sizes. To address the outliers and their impact on heterogeneity, a sensitivity analysis was performed by excluding the identified outlier (Study 3,7) and re-evaluating the heterogeneity metrics and pooled effect size. This will help determine the extent to which outliers influence the overall results.

After removing both Studies 3,7 (outlier) and Study 9 (largest contributor), the updated Forest plot is shown in Figure 6. It revealed a pooled effect size of 0.355, Between-study Variance (τ^2): 0.0000, Q statistic: 843.09, I^2 statistic: 98.8%. A high impact on study precision was observed with the original pooled standard error of 0.2218, corrected by 82.5% to 0.03.

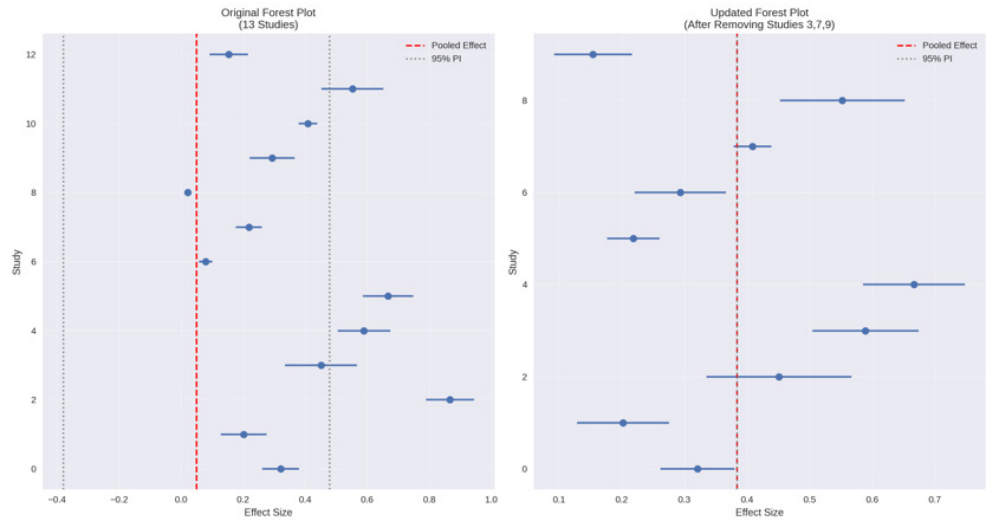

Figure 6: Comparison of forest plots original and update after removing three studies.

Despite removing the three studies, eight out of ten remaining studies still showed significant standardized residuals (|>2|), the between-study variance (τ^2) dropped to 0, and the standard error decreased by 82.5%, indicating more consistent effect estimates. Studies 6, 8, and 13 showed particularly large residuals (>|6|) and might represent genuine clinical heterogeneity.**Publication Bias Assessment:** Funnel Plot is shown in Figure 7. Egger's Test Results improved after the exclusion of the above studies and had an intercept of 0.5084; P = 0.3678 showed insignificant small study effects with mild bias. Heterogeneity reduction was seen in Tau^2 by 54.03% and in there was still substantial heterogeneity in the Identified Outliers in six studies with standardized residuals > |2.5|, ranging from -7.79 6.81. As shown in Table 4: These were excluded and a modified forest plot was generated (Figure 8). This showed substantial heterogeneity reduction with a slight decrease in the pooled effect size from 0.3822 to 0.3640, substantial reduction in Tau^2 from 0.0220 to 0.0034, I^2 decreased from 95.86% to 78.74%, Q statistic dramatically reduced from 217.44 to 14.11, and prediction intervals narrowed considerably (0.2309 to 0.4971). The final comparison of met data analysis between original group and final group is given in Table 4 which shows an improved model fit with final pool effect of 0.36 with narrowed prediction interval and moderate heterogeneity.

Table 4: Comparison of random-effects model after excluding outliers.

	Metric	Original Analysis	After Excluding Outliers
0	Pooled Effect	0.3822	0.364
1	Tauu00b2	0.022	0.0034
2	Iu00b2	95.8609	78.7363
3	Q Statistic	217.4367	14.1085
4	95% CI Lower	0.2872	0.2969
5	95% CI Upper	0.4773	0.4311
6	Prediction Interval Lower	0.0762	0.2309
7	Prediction Interval Upper	0.6883	0.4971

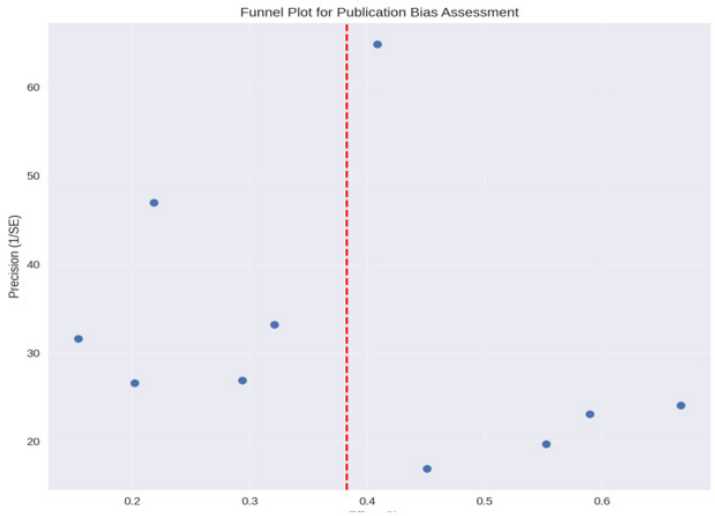

Figure 7: Funnel plot for publication bias after exclusion of studies.

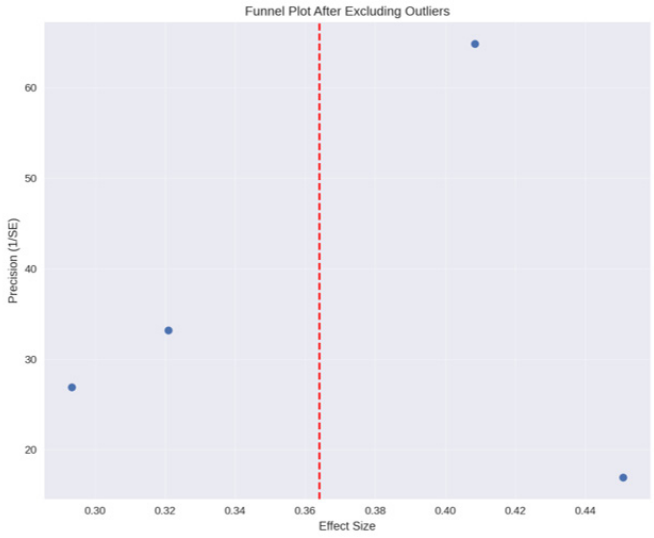

Figure 8: Funnel plot after excluding outliers.

Discussion

The meta-analysis revealed that atypical HCC nodules in patients with advanced chronic liver disease demonstrated a moderate pooled effect size of 0.36-0.3822 in both models, which is considered clinically significant and relevant to the diagnosis, as discussed separately below. High persistent heterogeneity was observed, ranging from 98% to 78% in both groups, indicating the necessity of implementing standardized reporting protocols to mitigate between-study heterogeneity. The findings of this study suggest that future research should aim for larger sample sizes as the analysis demonstrated more consistent effects in larger studies. Power calculations should target a minimum sample size based on a large subgroup (n > 376). Multicentre collaborations should be considered to increase sample size. Standardized reporting protocols should be implemented to reduce the between-study heterogeneity. Even after subgroup analysis and exclusion of the four studies, the heterogeneity remained at 78%. In the methodology of this study, the utilization of sensitivity analyses proved beneficial in accounting for potential outliers, and should be continued in future studies. Meta-regression with additional covariates should be incorporated in future studies to examine the effects of modifiers and factors contributing to the variation in effect sizes between small and large studies. The use of random-effects models for future meta-analyses should be maintained, and prediction intervals must be included in the results for high accuracy.

The secondary objective of this study was to define the clinical implications. A meta-analysis revealed a moderate pooled prevalence of 36% of atypical HCC nodules in patients with advanced chronic liver disease. This finding suggests that a significant proportion of HCC cases may not exhibit typical imaging features with the current diagnostic algorithms relying solely on typical contrast enhancement patterns (arterial hyperenhancement, portal venous

washout, and enhancing capsule) on CT/MRI, and may fail to identify up to one-third of HCC cases that present atypically [21]. This study advocates a more Bayesian approach to develop more robust models to improve diagnosis. Therefore, it is necessary to extend beyond the identification of typical imaging features. Some recommendations based on the findings of the current study are: a) implementation of standardized reporting protocols that account for both typical and atypical imaging presentations, and b) development and validation of more sophisticated diagnostic algorithms that incorporate multiple imaging tools and biochemical parameters, such as AFP-3, des-gamma-carboxy prothrombin (DCP), and GPC3 (Glypican-3) levels, which are overexpressed in HCC lesions [22-23]. Circulating tumor cells (CTCs) and cell-free DNA (cfDNA) have emerged as potential liquid markers for HCC detection [24]. Combining these markers into panels, such as the GALAD score, can also enhance the diagnostic accuracy of atypical HCC diagnosis [25]. Artificial intelligence techniques can be used to integrate these data to diagnose and predict nodules. From an imaging perspective, consideration should be given to the use of advanced MRI techniques such as diffusion-weighted imaging and hepatobiliary contrast agents (e.g., gadoxetic acid), which may improve the detection of atypical HCC compared with routine triple-phase CT and MRI imaging. The findings of the current study also emphasize the need for increased awareness of this morphology of HCC among both radiologists and hepatologists to prevent misdiagnosis and even consider shorter follow-up intervals for indeterminate nodules in high-risk patients.

In conclusion, atypical HCC nodules have a significant prevalence and there is a need to implement a comprehensive diagnostic approach to improve their detection and characterization, potentially leading to improved outcomes. However, new diagnostic strategies must be rigorously validated before widespread clinical implementation.

The limitations of the meta-analysis include high remaining heterogeneity (I^2 = 95.86%), potential small-study effects, a limited number of studies in some subgroups, and the possibility of unmeasured confounders.

Acknowledgement

None.

Conflict of Interest

None.

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