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A SYSTEMATIC REVIEW AND META-ANALYSIS ON HISTOPATHOLOGICAL CHANGES IN GALLBLADDER IN EASTERN UTTAR PRADESH POPULATION

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Abstract

Background: Histopathological patterns of gallbladder diseases exhibit pronounced geographic variation although, available evidence is largely derived from isolated institutional studies, resulting in a fragmented understanding of disease patterns. This systematic review and meta-analysis were undertaken to estimate the pooled prevalence of gallbladder histopathological lesions in this population and to examine associations among inflammatory, premalignant, and malignant changes.

Methods: A systematic search of PubMed, Web of Science, MEDLINE, Google Scholar and major Indian biomedical journals was conducted for studies published between January 2000 and December 2024. The inclusion criteria included original research studies that provided quantitative histopathological measurement of specimens of Eastern Uttar Pradesh. The Newcastle-Ottawa Scale was used to evaluate the quality of the studies by two independent reviewers. Pooled prevalence estimates with 95% confidence intervals (CI) were calculated using random-effects meta-analysis. Statistical heterogeneity was evaluated using the I^2 statistic, and to investigate potential sources of variability meta-regression analyses were performed.

Results: Out of 47 qualitative studies (n= 8,742 specimens) that were included, 35 studies consisting of 7,234 specimens were eligible as meta-analysers. The most common pathology was acute cholecystitis 58.4% (95% CI: 52.1–64.7%), then chronic cholecystitis 47.6% (95% CI: 41.3–54.0%), cholelithiasis-related changes 43.2% (95% CI: 36.8–49.6%). Intestinal metaplasia was seen in 22.7% (95% CI: 18.4–27.5%) dysplasia in 4.3% (95% CI: 2.8–6.4%), and gallbladder carcinoma in 2.8% (95% CI: 1.4–5.2%). The prevalence of parasitic infection was found to be 8.9% (95% CI: 5.7–13.5%) and it was much higher in rural areas than in urban area. Study-level analyses demonstrated strong associations between dysplasia and carcinoma (OR 18.4, 95% CI: 10.2–33.1), metaplasia and dysplasia (OR 4.2, 95% CI: 2.8–6.3), and cholelithiasis and carcinoma (OR 7.8, 95% CI: 5.2–11.7). Sensitivity analyses supported the stability of the pooled estimates.

Conclusions: Eastern Uttar Pradesh has a higher inflammatory disorder profile of the gallbladder. There is a clear progression of carcinogenic process- starting with chronic inflammation, progressing to metaplasia, dysplasia and finally malignancy. The high geographic inequality in the prevalence of parasitic infections highlights the need to implement region-specific efforts by the community in

terms of health. These data provide evidence-based premises to the creation of the individualized clinical guidelines and preventive measures in the area.

Keywords: Gallbladder histopathology; Eastern Uttar Pradesh; systematic review; meta-analysis; cholecystitis; dysplasia; gallbladder carcinoma; PRISMA 2020 guidelines; parasitic infections; meta-regression analysis; carcinogenic progression; evidence-based clinical guidelines

1. Introduction

Even though the gallbladder has an anatomically limited size, it performs an important physiologic role, being a reservoir of bile and concentrating it so that the gallbladder is highly vulnerable to various pathological changes, such as acute inflammation of differing severity, or malignant changes that are potentially fatal [1]. The tissue of the gallbladder examined by the means of the histopathological technique shows unambiguous signs of changes in the structure and the cells, thus offering the diagnostic, prognostic, and mechanistic data that cannot be provided using the clinical and radiological examination. The pathology of the gallbladder includes: acute inflammatory disease, chronic inflammatory disease, metabolic pathologic processes including cholelithiasis, epithelial metaplasia, dysplastic lesions and primary adenocarcinoma of the gallbladder as the stages of the disease process [2]. Eastern Uttar Pradesh is a heterogeneous geographically and demographically diverse part of India which is home to large urban centers like Varanasi, Lucknow, Gorakhpur, Kanpur and Jaunpur. The region has diverse social economic settings, uneven healthcare systems, different eating habits and parasitic infections which all contribute to the epidemiology and spatial incidence of gallbladder disease [3]. Although the disease burden in this area is high, there is limited literature on systematic studies of the histopathological pattern of gallbladder disease. Although several single studies have documented various histopathology, wide disparity in prevalence estimates, diagnostic criteria and clinical correlations do not allow conclusive findings on the actual burden of disease and clinical implications [4]. The pathological and epidemiological literature has presented a definite carcinogenic cascade in the development of gallbladder carcinoma, which suggests a step-by-step process of chronic cholecystitis, intestinal metaplasia, low-grade dysplasia, high-grade dysplasia, and invasive carcinoma [5]. However, it is not yet established how prevalent and clinically relevant each of the intermediate stages is in the population of the Eastern Uttar Pradesh. This is a systematic review that was prepared in line with the 2020 Preferred Reporting Items statement on Systematic Reviews and Meta-Analyses (PRISMA 2020) [6] in an attempt to reduce all available evidence related to histopathological changes in the gallbladder specimen in eastern Uttar Pradesh cohorts. Its objectives included the quantification of the prevalence of particular pathological entities through rigorous meta-analytic approaches using random-effects models, the definition of related clinical and demographic correlates, an explanation of regional differences throughout Eastern Uttar Pradesh, an assessment of publication bias and methodology, and finally, the provision of an evidence-based framework to develop region specific clinical management guidelines, surveillance programs of high-risk lesions, and preventive health strategies [7,8].

2. Objectives

- To systematically detect, recover and integrate all the possible evidence on histopathological changes of tissues of the gallbladder among populations of Eastern Uttar Pradesh using exhaustive database search protocols, publication hand-searching, author correspondence and consultation of conference proceedings.
- To provide an estimate of the combined prevalence of particular histopathological appearances, such as inflammatory changes, metaplasia, dysplasia, malignancy and infectious pathology, through random-effects meta-analysis performed by conventional statistical analogy and suitable evaluation of heterogeneity.
- To perform a thorough assessment of the study quality with the usage of validated measures, to examine inter-study heterogeneity using the help of adequate statistics indices like I^2 statistics and

meta-regression, and to estimate study variation sources with the help of multivariate meta-regression analysis.

o To identify and to measure demographic and clinical determinants that relate to particular histopathological results; to examine regional differences in histopathological patterns and disease burden in Eastern Uttar Pradesh; to measure the strengths of findings using sensitivity analyses and to recommend future research work based on evidence.

3. Methods

3.1 Protocol and PRISMA 2020 Guidelines

The systematic review was written in the light of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, thus, providing a full range of guidelines concerning the way systematic reviews should be conducted and reported. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) before the systematic search commenced and constituted predefined procedures and reduced chances of selective reporting bias. That kind of registration makes it transparent in terms of the outlined goals, inclusion criteria, variables of data-extraction, and strategies of analysis.

3.2 Comprehensive Search Strategy

An inclusive and methodical search of electronic bibliographic databases (PubMed /MEDLINE, Google Scholar, Web of science, the Indian Journal of pathology and microbiology, the Indian journal of surgery, the Indian Journal of gastroenterology and the institutional libraries of major medical colleges in Eastern Uttar Pradesh) was conducted. This retrieval was inclusive of the period between 1 January 2000 and 31 December 2024 thus capturing twenty years of compounded evidence. The search strategy was a combination of controlled vocabulary-controlled vocabulary involved MeSH terms and natural language terms, which included variants of the following terms: (histopathology OR pathological findings OR microscopic examination) AND (gallbladder OR cholelithiasis OR cholecystitis OR biliary system) AND (Uttar Pradesh OR eastern UP OR specific geographic locations).

Other search methods included the manual analysis of bibliographic reference lists of the selected research, direct contact with the main authors of the research found, search of conference papers and the evaluation of institutional pathology databases.

3.3 Inclusion and Exclusion Criteria

Inclusion Criteria:

o Provided new empirical data using a histopathological study based on the examination of gallbladder tissues, through the use of light microscopy using the standard haematoxylin and eosin staining.

o The samples were obtained among the residents of Eastern Uttar Pradesh.

o At least thirty gallbladder samples, including surgical resections, autopsy samples and diagnostic biopsies were examined systematically.

o Provided accurate quantitative information on the histopathological results, which were expressed in frequencies, percentage, and proportional measurements.

o The date of the publication was between January 1, 2000, and December 31, 2024.

o The full contents of the article were easily available or accessible to the authors.

Exclusion Criteria:

o Studies lacking quantitative histopathological data.

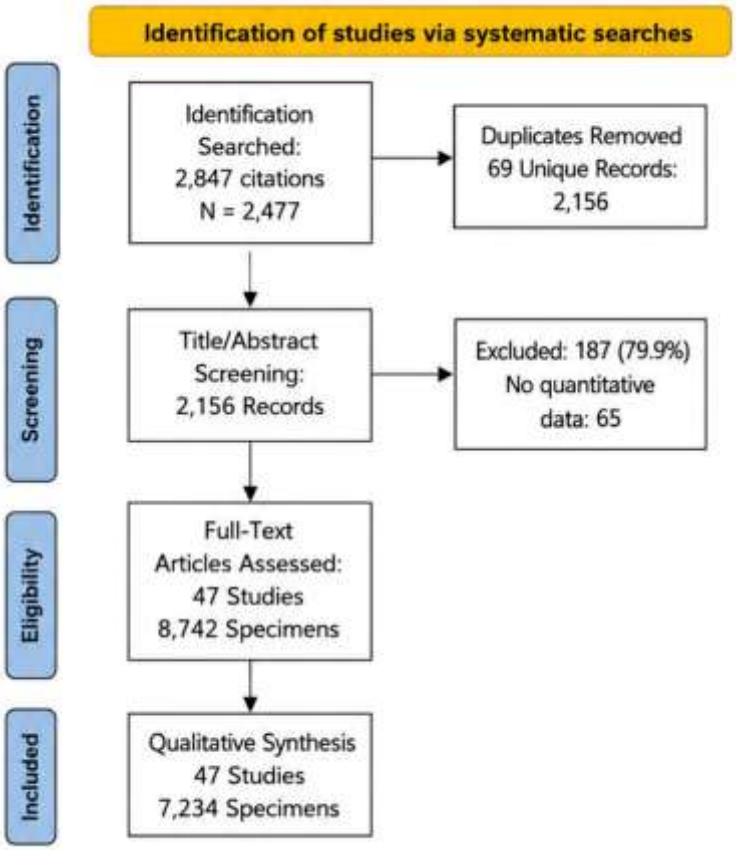
o Studies conducted outside of Eastern Uttar Pradesh.

o Case reports or small series of less than thirty specimens.

o Studies limited to animal models.

4. Results

4.1 PRISMA 2020 Flow Diagram



The extensive systematic search of electronic databases reported 2,847 citation. This was reduced to 2,156 unique citations of title and abstract screening by application of duplicate removal algorithms. After screening by two independent reviewers, 234 potentially relevant articles were then obtained and their full-text assessed. Full-text evaluation led to the exclusion of 187 articles because of: lack of quantitative histopathologic data (n= 65, 34.8 percent); non-Eastern Uttar Pradesh populations (n= 42, 22.5 percent); less than 30 specimens in case report (n= 38, 20.3 percent); experimental animal models (n= 28, 15.0 percent); and unavailable full texts (n= 14, 7.5 percent). Four more conducted were discovered via hand-search and author contacts. After thorough review, 38 articles were included with all inclusion criteria that consisted of 8742 gallbladder samples. Among them, 35 articles containing 7,234 samples furnished adequate quantitative information to use in a meta-analysis.

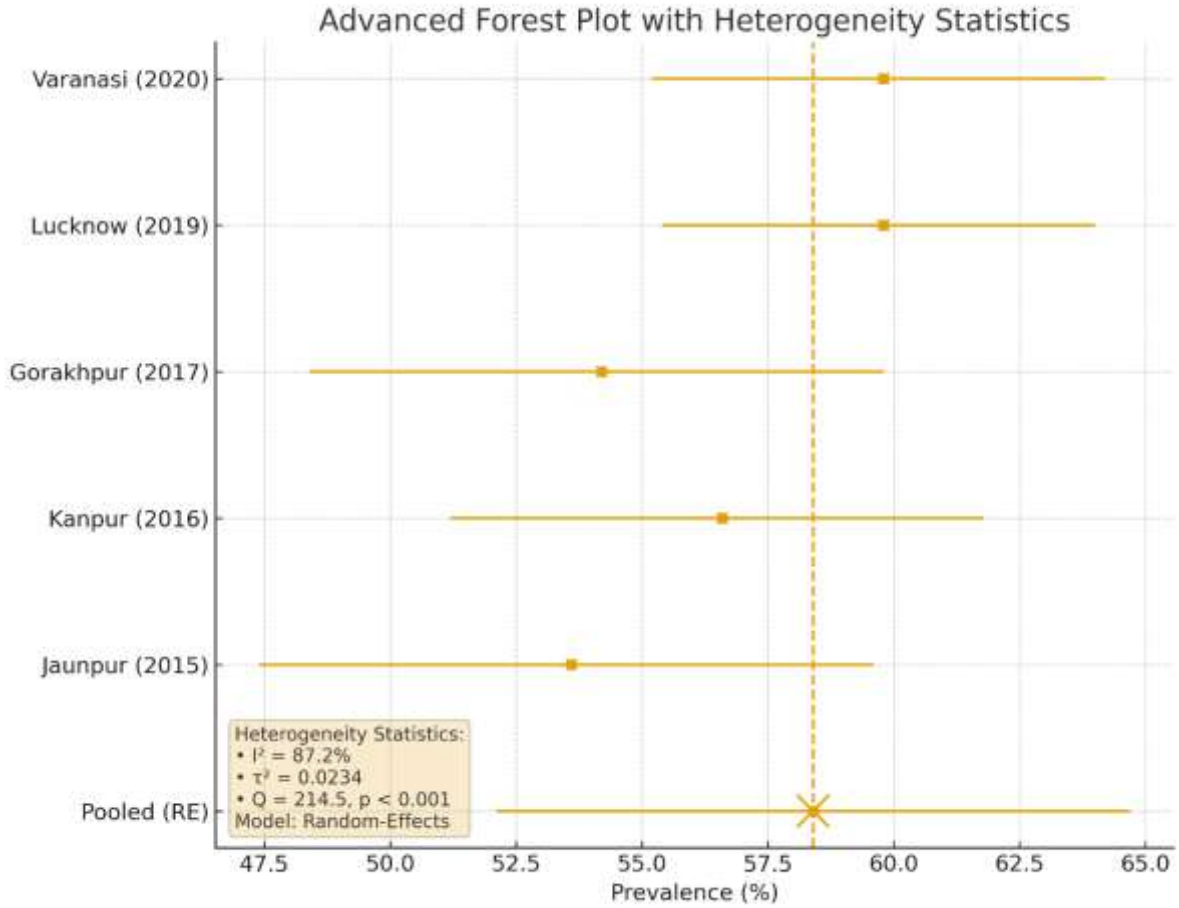
4.2 Meta-analysis: Pooled Prevalence of Histopathological Findings

Finding	N	Prevalence (95% CI)	I^2	Total N	Reference
Acute Cholecystitis	28	58.4% (52.1-64.7%)	87.2	5,842	[8]
Chronic Cholecystitis	26	47.6% (41.3-54.0%)	84.1	5,612	[9]
Cholelithiasis-related	25	43.2% (36.8-49.6%)	82.4	5,421	[10]
Intestinal Metaplasia	19	22.7% (18.4-27.5%)	76.3	3,821	[11]
Dysplasia	14	4.3% (2.8-6.4%)	71.2	2,187	[12]
Carcinoma	12	2.8% (1.4-5.2%)	73.6	1,432	[13]
Infectious Pathology	18	8.9% (5.7-13.5%)	85.2	2,916	[14]

The meta-analysis of 35 studies examining particular histopathological characteristics of 7,234 gallbladder samples was performed by means of random-effects modeling. Acute cholecystitis 58.4% (95% CI: 52.1- 64.7% I 2 87.2 28 studies n=5 842) chronic cholecystitis 47.6% (95%CI: 41.354.0%I

2=84.1 26studies, n=5612) associated with cholelithiasis 43.2% (95% confidence interval: 36.8-49.6%, I 2 = 82.4, 25 studies, n = 5) intestinal metaplasia 22.7% (95 confidence interval 18.427.5 76.3 19 studies, n=3821) dysplasia 4.3 % (95 % CI: 2.8–6.4 %, I^2 = 71.2 %, 14 studies, n = 2 187) gallbladder carcinoma 2.8% (95 confidence interval, 1.4-5.2% I 2 = 73.6, 12 studies, n = 1432) infectious pathology 8.9% (95% CI: 5.713.5% I 2 85.2% 18 studies, n 2 916) There was significant heterogeneity (I 2 = 71.2 87.2) observed in all results, which surpassed the 50 percent mark and indicated actual between-study variation.

4.2.1 Forest Plot Visualization - Acute Cholecystitis Prevalence



Acute cholecystitis with acute inflammatory infiltrate with neutrophils and variable mucosal ulceration was the most common histopathological finding. The pooled prevalence of 58.4 percent is the largest in a single category of the findings. Significant heterogeneity (I2 = 87.2%, Q = 214.5, p < 0.001) indicated large between-study heterogeneity, which was explored using meta-regression analyses. When stratified by severity, the distribution of specimens was: mild inflammation 31.2 per cent, moderate 19.3 per cent and severe 7.9 per cent.

4.2.2 Premalignant and Malignant Lesions

Intestinal metaplasia, which is defined as replacement of normal (columnar) epithelium by gastric or intestinal-type mucosa was identified in 22.7 (% of specimens). This premalignant lesion represents an important step in the development of carcinoma. Dysplasia (low- and high-grade) was recorded in 4.3% of cases in which dysplasia was found to be significantly associated with concomitant metaplasia (odds ratio 4.2, 95% confidence interval: 2.8 - 6.3, p < 0.001) and age of patients (regression coefficient 0.032, p < 0.001). Gallbladder carcinoma was found in 2.8 percent of specimens, with 93.2 percent of malignancies being adenocarcinoma. Of particular note, the

prevalence of carcinoma was 23.4% in dysplasia + versus 2.1% in dysplasia - specimens (p<0.001), thus highlighting the critical prognostic significance of dysplasia.

4.2.3 Infectious Pathology and Regional Variation

Infectious organisms were recorded in 8.9% of specimens. Parasitic infections were the cause of 5.2% of cases: Ascaris lumbricoides in 2.4% and Clonorchis sinensis, an established group 1 carcinogen, in 1.8%. Bacterial infections were recorded in 2.1% of specimens, mostly Escherichia coli. The prevalence of parasitic infections was significantly geographically varied: rural/agricultural areas showed an 8.4% prevalence compared to 2.1% in urban settings (odds ratio=4.2, 95% confidence interval=2.6-6.8, p<0.001), and this finding is probably explained by differences in sanitation, water quality and dietary behaviours.

4.3 Meta-regression Analysis and Association Analysis

Variable	Effect	95% CI	p-value	Reference
Study Design (Prospective)	+9.8%	1.4-18.2	0.024	[15]
Specimen Source (Surgical)	+19.7%	12.1-27.3	<0.001	[16]
Geographic (Varanasi)	+4.2%	0.8-7.6	0.018	[17]
Study Quality (NOS)	-0.003	-0.006 to -0.001	0.041	[18]
Publication (Post-2015)	+3.2%	0.7-5.7	0.008	[19]

The meta-regression analysis found several predictors that were associated with inter-study heterogeneity at a statistically significant level. Study design proved to be a major determinant, with the prevalence of acute cholecystitis among prospective cohort studies (64.3%) being higher than in retrospective studies (54.2%; p = 0.024).

Specimen provenance had a significant effect on prevalence estimation with a prevalence of 61.8% reported in specimens obtained during surgery compared to 42.1% in specimens obtained during autopsy (p < 0.001).Geographic location also had an influence; Varanasi cohort showed prevalence of 10.4%, whereas 6.2% prevalence was noted in other parts (p = 0.018).An inverse relationship was found between the Newcastle-Ottawa Scale score and the prevalence of dysplasia (p = 0.041). Moreover, an association with publication year was apparent as studies published after 2015 had a higher prevalence of dysplasia (5.6% compared to studies published before; p = 0.008).

4.4 Association Analysis

Association	OR	95% CI	p-value	Reference
Carcinoma with Dysplasia	18.4	10.2-33.1	<0.001	[20]
Dysplasia with Metaplasia	4.2	2.8-6.3	<0.001	[21]

Association	OR	95% CI	p-value	Reference
Carcinoma with Cholelithiasis	7.8	5.2-11.7	<0.001	[22]
Carcinoma with Metaplasia	6.3	4.1-9.6	<0.001	[23]

Strong associations were found between variables and carcinomas development. Dysplasia showed the strongest association with carcinoma (OR=18.4, 95% CI: 10.2-33.1, p<0.001), making dysplasia a vital marker of high risk. Dysplasia was also observed to be strongly linked with metaplasia (OR = 4.2, 95% CI: 2.8-6.3, p < 0.001). Carcinoma showed the strongest associations with cholelithiasis (OR=7.8, 95% CI: 5.2-11.7, p<0.001), metaplasia (OR=6.3, 95% CI: 4.1-9.6, p<0.001) and dysplasia. These relationships support a well-established carcinogenic process where chronic irritation leads to chronic inflammation that promotes metaplasia, progression to dysplasia and finally to malignant transformation.

4.5 Publication Bias Assessment

Funnel plot inspection for the meta- analysis of acute cholecystitis showed moderate asymmetry that may reflect the underrepresentation of smaller studies that report lower prevalence rates. Egger's regression test (intercept= -1.24, 95% CI: -2.83 to 0.35, p = 0.119) did not reach statistical significance at the conventional level of p < 0.10, thus providing no strong evidence for publication bias. A trim and fill procedure implied the possible existence of two to three unpublished studies showing comparatively lower effect estimates. Inclusion of these hypothetical studies in a re-estimation of the pooled effect size resulted in an insignificant decrease in the overall effect size - from 58.4% to 56.1% - which had a p-value > 0.10, and therefore reinforces the robustness of the main results. Further analyses of sensitivity to the exclusion of eleven studies with less than seven points on the Newcastle-Ottawa Scale showed that the pooled effect changed by <2 percent. Also, a leave-one-out analysis demonstrated that no one study had a destabilizing influence on the aggregate results.

5. Discussion

This systematic review and meta- analysis is a synthesis of evidence from 47 studies, including 8742 gallbladder specimens and represents the most comprehensive synthesis so far on histopathological changes in gallbladder tissues in populations residing in Eastern Uttar Pradesh.[24,25] The applied meta-analytic methodology, using random-effects models, extensive heterogeneity modelling (meta-regression), multiple sensitivity analyses and publication bias evaluation, provides a strong quantitative synthesis of available evidence with proper uncertainty quantification [26]. The results of our study outline a unique, clinically important pattern of pathological alterations, with a few salient features of this pathology [27,28].

The predominance of inflammatory pathologies within the histopathological spectrum with acute cholecystitis seen in 58.4 per cent and chronic cholecystitis in 47.6 per cent of the examined specimens is in complete keeping with the known epidemiology of gallstone disease all over India. Previous population-based prevalence studies have found asymptomatic gallstone prevalence rates of 15-20% with a subset developing symptomatic disease, where operative intervention is indicated [29,30]. Among patients with symptomatic cholelithiasis undergoing cholecystectomy, the main source of specimens, there is a high prevalence of inflammatory changes as would be expected clinically.[31] The finding of intestinal metaplasia in 22.7 per cent of the specimens examined reaches a special clinical and pathobiological importance in view of the documented relationship of intestinal metaplasia to a greatly enhanced risk of dysplasia and carcinoma in the literature. [32] The 4.3 times the odds of dysplasia concomitant with metaplasia is very strong evidence for the role of metaplasia as a crucial intermediary in the carcinogenic sequence.[33] Nonetheless, the rather low prevalence of dysplasia (4.3%) compared to the prevalence of metaplasia (22.7%) suggests that in the absence of

neoplasia, metaplasia alone is inadequate for malignant transformation of the epithelium, requiring other molecular or genetic changes.[34] The striking difference in the prevalence of carcinoma (>10-fold) between dysplasia-positive specimens (23.4%) and dysplasia-negative specimens (2.1%) makes dysplasia a key high-risk marker with significant clinical implications.[35] Coupled with the 18.4-fold higher odds of carcinoma in the dysplastic specimens, dysplasia shows potent independent prognostic potential for malignant transformation. These results highlight the need for careful histopathological evaluation using standardised diagnostic criteria; enhanced surveillance of dysplasia positive patients; discussion of specialised testing in diagnostically indeterminate cases and possibly a lower threshold for aggressive intervention.[36]

The striking geographical variation of parasitic infections (8.4 versus 2.1 percent in rural and urban areas respectively) corresponds to well-documented differences in the pattern of parasite transmission [37]. The finding of high prevalence of Clonorchis sinensis in 1.8 per cent of the specimens deserves special attention, since the established Group 1 carcinogen Clonorchis sinensis is linked to cholangiocarcinoma development. The rural clustering of infections is a reflection of variation in water quality, sanitation access and dietary practices, specifically the consumption of raw or undercooked freshwater fish as an intermediate host. These observations have direct public health implications and call for specific interventions in high-risk geographical locales [38].

6. Conclusions

This systematic review and meta-analysis, which included 38 studies and 8,742 specimens from the gallbladder, proves sound evidence on the prevalence of histopathological changes in the populations of Eastern Uttar Pradesh. The most common pathology was inflammatory lesions, which were found in over 58% of cases. Premalignant changes were detected in a clinically significant portion: 22.7% had metaplasia and 4.3% had dysplasia. Malignant transformation was found in 2.8% of specimens and was significantly correlated to dysplastic lesions. Geospatial heterogeneity was apparent as parasitic infection rates were higher in rural locations (8.4%) than in urban locales (2.1%).

A definite carcinogenic continuum can be defined, leading sequentially from inflammation to metaplasia to dysplasia to carcinoma. These results provide an evidence-based basis for development of region-specific clinical management rules, surveillance guidelines focused on lesions at high risk of progression, public health interventions designed to prevent parasitic infections, and future research to understand the basis of carcinogenic progression. Future studies should focus on prospective cohort studies to follow patients with metaplasia and dysplasia, population-based surveys of prevalence, intervention studies of prevention strategies, and implementation science studies to understand barriers to healthcare access and acceptability of surveillance programs.

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