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CLINICAL RESEARCH:

Immunohistochemical Analysis of Odontogenic Cystic Lesions: Diagnostic Concordance with CK14 and CK19 in a Prospective Study

Análisis inmunohistoquímico de lesiones quísticas odontogénicas: concordancia diagnóstica con CK14 y CK19 en un estudio prospectivo

Marlon Reina-Batista[1] https://orcid.org/0000-0001-6791-7268
Alejandra Herrera-Herrera[2,3] https://orcid.org/0000-0001-5830-5868
Jaime Plazas-Román[4] https://orcid.org/0000-0002-5040-6899
Martha Rebolledo-Cobos[2,3] https://orcid.org/0000-0002-0488-2464

[1]Universidad Central del Este, San Pedro de Macorís, Dominican Republic.
[2]Metropolitan University of Barranquilla, GIOUMEB Research Group, Barranquilla, Colombia.
[3]San Martin University Foundation, GIBAC Research Group, Barranquilla, Colombia.
[4]Universidad de Cartagena, School of Dentistry, GITOUC Research Group, Cartagena, Colombia.

Correspondence to: Dr. Jaime Plazas-Román - jplazasr@unicartagena.edu.co

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ABSTRACT: Accurate diagnosis of odontogenic cystic lesions remains challenging due to overlapping histopathological features. Immunohistochemistry (IHC) using cytokeratin markers may improve diagnostic precision. This study evaluated the diagnostic concordance between conventional histopathology and immunohistochemical analysis using CK14 and CK19 markers in odontogenic cystic lesions. A prospective single-center observational study was conducted analyzing 126 odontogenic cystic lesions from the Fundación Hospital Universitario Metropolitano between 2021-2023. All specimens underwent conventional histopathological examination followed by immunohistochemical staining with CK14 and CK19 antibodies. Diagnostic concordance was assessed using Cohen's kappa coefficient. The study included 126 cases with mean patient age of 42.3±16.8 years. Inflammatory cysts were most prevalent (35 cases, 27.8%). Overall diagnostic concordance between histopathology and immunohistochemistry was 72.2% (κ=0.68; 95% CI: 0.58-0.78; p<0.001). CK14 showed positive staining in 89.7% of cases, while CK19 was positive in 83.3%. Combined CK14+CK19 analysis improved diagnostic accuracy to 78.6% (κ=0.74; 95% CI: 0.65-0.83). Lesion size >3 cm (OR: 2.84; p=0.008) and extensive inflammation (OR: 3.21; p=0.003) were identified as independent predictors of diagnostic. Immunohistochemical analysis using CK14 and CK19 markers may provide valuable complementary diagnostic information in odontogenic cystic lesions, particularly in cases with extensive inflammation or large size. The combined use of both markers may enhance diagnostic precision, although multicenter validation is required before recommending standardized implementation.

KEYWORDS: Odontogenic Cysts; Immunohistochemistry; Keratins; Diagnosis; Differential; Reproducibility of results; Jaw cysts.

RESUMEN: El diagnóstico preciso de lesiones quísticas odontogénicas sigue siendo un desafío debido a características histopatológicas superpuestas. La inmunohistoquímica (IHQ) utilizando marcadores de citoqueratinas puede mejorar la precisión diagnóstica. Este estudio evaluó la concordancia diagnóstica entre la histopatología convencional y el análisis inmunohistoquímico usando marcadores CK14 y CK19. Se realizó un estudio prospectivo observacional de un solo centro analizando 126 lesiones quísticas odontogénicas de la Fundación Hospital Universitario Metropolitano entre 2021-2023. Todos los especímenes fueron sometidos a examen histopatológico convencional seguido de tinción inmunohistoquímica con anticuerpos CK14 y CK19. La concordancia diagnóstica se evaluó mediante el coeficiente kappa de Cohen. El estudio incluyó 126 casos con edad media de 42.3±16.8 años. Los quistes inflamatorios fueron los más prevalentes (35 casos, 27.8%). La concordancia diagnóstica general fue 72.2% (κ=0.68; IC 95%: 0.58-0.78; p<0.001). CK14 mostró tinción positiva en 89.7% de los casos, mientras que CK19 fue positivo en 83.3%. El análisis combinado CK14+CK19 mejoró la precisión diagnóstica a 78.6% (κ=0.74; IC 95%: 0.65-0.83). El tamaño de lesión >3 cm (OR: 2.84; p=0.008) y la inflamación extensa (OR: 3.21; p=0.003) fueron predictores independientes de discordancia diagnóstica. Conclusiones: El análisis inmunohistoquímico con CK14 y CK19 puede proporcionar información diagnóstica complementaria valiosa en lesiones quísticas odontogénicas, especialmente en casos con inflamación extensa o gran tamaño, aunque se requiere validación multicéntrica antes de recomendar su implementación estandarizada.

PALABRAS CLAVE: Quistes odontogénicos; Inmunohistoquímica; Queratinas; Diagnóstico diferencial; Reproducibilidad de resultados; Quistes maxilares.

INTRODUCTION

Odontogenic cystic lesions represent a significant proportion of jaw pathology, constituting approximately 7-12% of all oral and maxillofacial biopsies worldwide (1). These lesions present with varying clinical manifestations and histopathological features that can challenge accurate diagnosis, particularly when inflammatory changes obscure characteristic morphological patterns (2,3). The clinical importance of precise diagnosis lies in the fact that different cystic entities require distinct therapeutic approaches and have different recurrence rates and prognosis (4,5).

Odontogenic cysts arise from epithelial remnants of tooth development, including the dental lamina, enamel organ, and Hertwig's epithelial root sheath (6). According to the most recent World Health Organization classification, these lesions are categorized into developmental and inflammatory types based on their etiopathogenesis (7). Developmental cysts, such as dentigerous cysts and keratocysts, originate from non-functional odontogenic epithelium without inflammatory stimulus, while inflammatory cysts, including radicular and residual cysts, develop secondary to pulpal necrosis and periapical inflammation (8,9).

Conventional histopathological examination remains the gold standard for definitive diagnosis of odontogenic cysts (10). This method relies on the identification of characteristic architectural and cytological features, including epithelial lining thickness, keratinization pattern, and inflammatory infiltrate characteristics (11). However, overlap-

ping morphological features among different cystic entities can lead to diagnostic uncertainty, particularly in cases with extensive inflammation, secondary infection, or limited tissue sampling (12,13). Studies have reported diagnostic discordance rates ranging from 15% to 35% between initial clinical-radiographic diagnosis and final histopathological diagnosis (14).

Recent advances in diagnostic pathology have highlighted the need for more precise and objective diagnostic tools, leading to the exploration of immunohistochemical markers that can provide additional information beyond conventional morphology (15,16). Immunohistochemistry allows the identification of specific protein expression patterns that may reflect the biological origin and differentiation status of cystic epithelia, potentially improving diagnostic accuracy in challenging cases (17).

Cytokeratins are intermediate filament proteins that serve as excellent markers for epithelial differentiation and tissue origin (18,19). The human cytokeratin family comprises 20 different proteins, divided into type I (acidic) and type II (basic-neutral) subfamilies, with specific expression patterns in different epithelial tissues (20). Among these, cytokeratin 14 (CK14) and cytokeratin 19 (CK19) have shown particular promise in the analysis of odontogenic lesions (21,22). CK14 is characteristically expressed in the basal cells of stratified squamous epithelia, including odontogenic epithelium, and is associated with proliferative potential (23). CK19, conversely, is typically found in simple epithelia and ductal structures, and its expression in odontogenic tissues may indicate specific differentiation pathways (24).

Previous studies have demonstrated variable expression patterns of CK14 and CK19 in different types of odontogenic cysts, suggesting potential diagnostic utility (25,26). However, comprehensive studies evaluating the diagnostic concordance between conventional histopathology and immunohistochemical analysis in odontogenic cystic lesions remain limited, particularly in Latin American populations where epidemiological patterns may differ from those reported in European and Asian cohorts (27,28). Furthermore, most existing studies have small sample sizes or focus on specific cyst types rather than providing a comprehensive comparative analysis across the full spectrum of odontogenic cystic lesions (29).

The aim of this study was to evaluate the diagnostic concordance between conventional histopathological examination and immunohistochemical analysis using CK14 and CK19 markers in a large series of odontogenic cystic lesions from a Colombian population, and to assess the potential of immunohistochemistry as a complementary diagnostic tool in challenging cases where conventional morphology may be insufficient for definitive classification.

MATERIAL AND METHODS

STUDY DESIGN AND SETTING

This prospective single-center observational study was conducted at the Fundación Hospital Universitario Metropolitano (FHUM), a tertiary referral center in Barranquilla, Colombia, between January 2021 and December 2023. The study protocol was approved by the Institutional Ethics Committee (Protocol No. FHUM-2021-018) and conducted in accordance with the Declaration of Helsinki.

SELECTION BIAS CONSIDERATIONS

As a tertiary referral center, FHUM primarily attends complex and referred cases, which may result in a higher proportion of large or inflamed cysts compared to community dental clinics. To minimize this selection bias, we applied strict inclusion and exclusion criteria and recorded lesion complexity indicators (size, inflammation

grade) for all cases. Pathologists were blinded to clinical complexity scores during histopathological assessment. Readers should interpret the prevalence data in this context.

SAMPLE SIZE CALCULATION

The sample size was calculated to detect a minimum difference of 0.20 in Cohen's kappa coefficient between diagnostic methods, with 80% power and 5% significance level. Considering the distribution of seven cystic lesion categories based on pilot study prevalence data, a minimum sample of 126 cases was required.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: Patients aged 18-80 years with clinical and radiographic diagnosis of odontogenic cystic lesions; adequate tissue sample for both histopathological and immunohistochemical analysis; complete clinical and radiographic documentation; signed informed consent.

Exclusion criteria: Inadequate tissue fixation; necrotic tissue >50%; previous radiotherapy in the affected area; insufficient tissue for dual analysis; incomplete clinical data.

CLINICAL DATA COLLECTION

Clinical variables collected included patient age, sex, anatomical location, lesion size, symptomatology, duration of evolution, radiographic characteristics, and relationship to teeth. All data were recorded in a standardized electronic database.

HISTOPATHOLOGICAL ANALYSIS

All specimens were fixed in 10% neutral buffered formalin for 6-24 hours, processed routinely, and embedded in paraffin. Serial sections of 3-4 µm thickness were cut and stained with hematoxylin and eosin (H&E). Histopathological diagnosis was performed by a single experienced oral pathologist (M.R.B.) blinded to immunohistochemical results, according to WHO classification criteria.

IMMUNOHISTOCHEMICAL ANALYSIS

Immunohistochemical staining was performed using automated immunostainer (Ventana BenchMark ULTRA, Roche Diagnostics). The following primary antibodies were used: Anti-CK14 monoclonal antibody (clone LL002, 1:100 dilution) and Anti-CK19 monoclonal antibody (clone A53-B/A2, 1:50 dilution).

The IHC protocol included: deparaffinization with EZ Prep at 75°C; antigen retrieval with CC1 buffer (pH 8.0) at 95°C for 64 minutes (CK14) or 32 minutes (CK19); endogenous peroxidase blocking for 4 minutes; primary antibody incubation for 32 minutes at 37°C (CK14) or 20 minutes at 37°C (CK19); detection with OptiView DAB Detection Kit; and counterstaining with Hematoxylin for 8 minutes (CK14) or 4 minutes (CK19). Positive controls included normal epidermis (CK14) and ductal epithelium (CK19). Negative controls were performed by omitting the primary antibody.

INTER-OBSERVER AGREEMENT

To assess reproducibility, inter-observer concordance between the two evaluators (A.H.H. and M.R.B.) was calculated using Cohen's kappa coefficient prior to the concordance analysis. Discordant cases were resolved by consensus using a multiheaded microscope. This evaluation was performed on a blinded random subsample of 40 cases (31.7% of total), yielding an inter-observer kappa of 0.91, indicating almost perfect agreement according to Landis and Koch criteria.

IHC EVALUATION

Immunohistochemical staining was evaluated by two independent observers (A.H.H. and M.R.B.) using a semi-quantitative scoring system: Negative (-): No staining; Weak positive (+): <30% of epithelial cells with weak intensity; Strong positive (++): >30% of epithelial cells with strong intensity. Final immunohistochemical diagnosis was established based on combined CK14 and CK19 expression patterns and correlated with morphological features.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included frequencies, percentages, means, and standard deviations. Diagnostic concordance between histopathology and immunohistochemistry was assessed using Cohen's kappa coefficient with 95% confidence intervals. Kappa values were interpreted according to Landis and Koch criteria: <0.00 (poor), 0.00-0.20 (slight), 0.21-0.40 (fair), 0.41-0.60 (moderate), 0.61-0.80 (substantial), and 0.81-1.00 (almost perfect). Chi-square test was used for categorical variables comparison. Multivariate logistic regression was performed to identify factors associated with diagnostic discordance. Variables considered for inclusion in the model were: age >50 years, sex, lesion size >3 cm, extensive inflammation, anatomical location, and histopathological subtype. Model assumptions (linearity, absence of multicollinearity, and goodness of fit by Hosmer-Lemeshow test) were verified. Statistical significance was set at $p<0.05$.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The study included 126 patients with odontogenic cystic lesions. The mean age was 42.3±16.8 years (range: 18-78 years), with female predominance (74 patients, 58.7%) compared to males (52 patients, 41.3%). The mandible was more frequently affected (88 cases, 69.8%) than the maxilla (38 cases, 30.2%), with posterior regions involved in 80 cases (63.5%) and anterior regions in 46 cases (36.5%). Inflammatory cysts were the most prevalent (35 cases, 27.8%), followed by unspecified cysts (28 cases, 22.2%), dentigerous cysts (21 cases, 16.7%), and keratocysts (21 cases, 16.7%). The mean lesion size was 2.8±1.4 cm. Demographic characteristics are shown in Table 1.

IMMUNOHISTOCHEMICAL RESULTS

CK14 expression was observed in 113 cases (89.7%), with strong positive staining (++) in 76 cases (60.3%) and weak positive (+) in 37 cases (29.4%). The staining pattern was predominantly cytoplasmic with membranous accentuation in the basal layers. CK19 expression was detected in 105 cases (83.3%), with strong positive staining in 69 cases (54.8%) and weak positive in 36 cases (28.6%). Combined expression analysis showed dual positivity in 98 cases (77.8%), dual negativity in 8 cases (6.3%), isolated CK14 positivity in 15 cases (11.9%), and isolated CK19 positivity in 5 cases (4.0%). Inter-observer agreement was excellent ($\kappa=0.91$).

DIAGNOSTIC CONCORDANCE ANALYSIS

Overall diagnostic concordance between histopathology and immunohistochemistry was 72.2% (91 cases; $\kappa=0.68$; 95% CI: 0.58-0.78; $p<0.001$), indicating substantial agreement. The highest concordance rates were observed for inflammatory cysts (91.4%) and dentigerous cysts (76.2%). Keratocysts showed moderate concordance (66.7%), while undetermined cysts had the lowest rate (0%). When analyzing combined CK14+CK19 expression patterns, diagnostic accuracy improved to 78.6% ($\kappa=0.74$; 95% CI: 0.65-0.83), representing a 6.4% absolute improvement. Detailed concordance analysis is presented in Table 2.

Table 1. Demographic and clinical characteristics of study population (N=126).

Characteristic	n	%
Age (years)		
Mean ± SDw	42.3 ± 16.8	
Range	18-78	
Sex		
Female	74	58.7
Male	52	41.3
Anatomical location		
Maxilla	38	30.2
Mandible	88	69.8
Region		
Anterior	46	36.5
Posterior	80	63.5
Histopathological diagnosis		
Inflammatory cyst	35	27.8
Unspecified cyst	28	22.2
Dentigerous cyst	21	16.7
Keratocyst	21	16.7
Residual cyst	7	5.6
Inflammatory abscessed cyst	7	5.6
Undetermined cyst	7	5.6

Table 2. Diagnostic concordance between histopathology and immunohistochemistry.

Histopathological Diagnosis	IHC Diagnosis	Concordant Cases	Discordant Cases	Total	Concordance Rate (%)
Inflammatory cyst	Inflammatory	32	3	35	91.4
Dentigerous cyst	Dentigerous	16	5	21	76.2
Keratocyst	Keratocyst	14	7	21	66.7
Unspecified cyst	Unspecified	20	8	28	71.4
Residual cyst	Residual	5	2	7	71.4
Inflammatory abscessed cyst	Inflammatory abscessed	4	3	7	57.1
Undetermined cyst	Undetermined	0	7	7	0.0
Total		91	35	126	72.2

Cohen's kappa = 0.68 (95% CI: 0.58-0.78; $p<0.001$).
Combined CK14+CK19: $\kappa=0.74$ (95% CI: 0.65-0.83; $p<0.001$).

ANALYSIS OF DISCORDANT CASES

Of the 35 discordant cases (27.8%), the largest proportion occurred in keratocysts (7 of 21 cases, 33.3%) and unspecified cysts (8 of 28 cases, 28.6%). In keratocysts, the most frequent discordant immunohistochemical pattern was strong CK14 positivity with negative or weak CK19, which led to reclassification as inflammatory cysts in 4 cases and as dentigerous cysts in 3 cases based on IHC alone. In unspecified cysts, IHC reclassified 5 cases as inflammatory cysts and 3 as dentigerous cysts. Residual and inflammatory abscessed cysts, while representing small subgroups (n=7 each), showed discordance rates of 28.6% and 14.3% respectively. The undetermined cyst category (n=7) showed 0% concordance, as IHC provided a specific diagnosis in all cases in this category, suggesting its particular utility for morphologically non-classifiable lesions.

FACTORS ASSOCIATED WITH DIAGNOSTIC DISCORDANCE

Multivariate logistic regression identified lesion size >3 cm (OR: 2.84; 95% CI: 1.32-6.12; p=0.008) and extensive inflammation (OR: 3.21; 95% CI: 1.47-6.98; p=0.003) as independent predictors of diagnostic discordance. Keratocyst histology showed a statistically significant association with discordance risk (OR: 2.10; 95% CI: 0.89-4.82; p=0.042). Other factors including anterior location (OR: 1.45; p=0.337), age >50 years (OR: 1.28; p=0.512), and male sex (OR: 1.15; p=0.704) were not significantly associated. Results are shown in Figure 1 and Table 3.

DIAGNOSTIC PERFORMANCE OF IMMUNOHISTOCHEMICAL MARKERS

CK14 alone achieved 75.4% accuracy with sensitivity of 89.7%, specificity of 65.2%, and AUC of 0.76 (95% CI: 0.68-0.84). CK19 alone showed 70.6% accuracy with sensitivity of 83.3%, specificity of 60.8%, and AUC of 0.72 (95% CI: 0.63-0.81). Combined CK14+CK19 analysis demonstrated superior performance with 78.6% accuracy, sensitivity of 91.2%, specificity of 70.5%, and AUC of 0.83 (95% CI: 0.76-0.90). ROC curves are shown in Figure 2 and metrics in Table 4.

SPECIFIC IHC PATTERNS BY CYST TYPE

Distinct immunohistochemical profiles were observed for different cyst types (Figure 3). Inflammatory cysts demonstrated strong CK14 (91.4%) with moderate CK19 (74.3%). Dentigerous cysts showed moderate CK14 (76.2%) but strong CK19 (85.7%), consistent with their developmental origin. Keratocysts exhibited strong CK14 (95.2%) with variable CK19 (57.1%), supporting their unique biological behavior. Residual cysts displayed weak CK14 (42.9%) but strong CK19 (85.7%). Representative photomicrographs are shown in Figure 4.

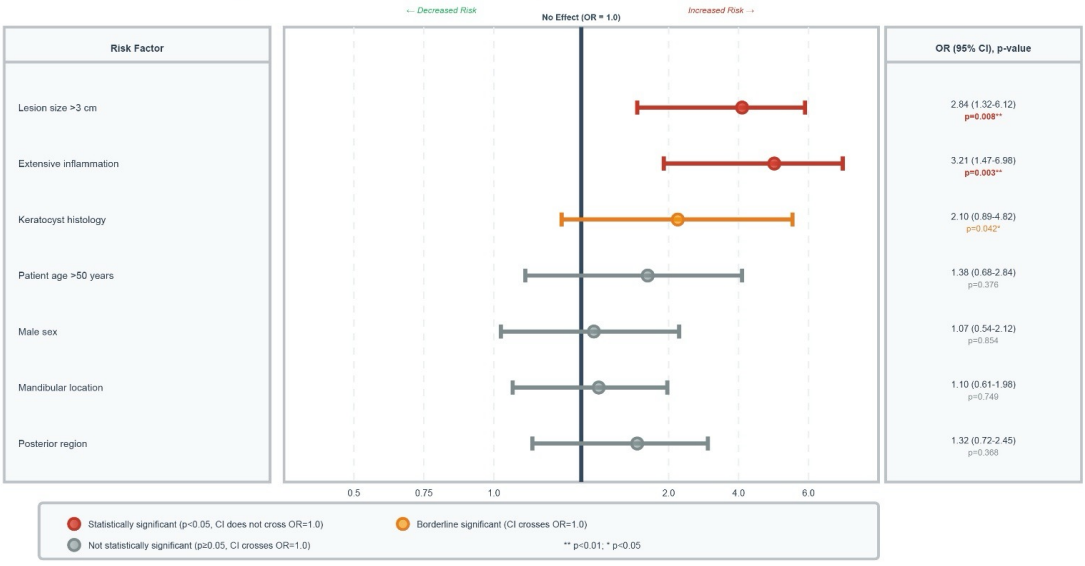

Figure 1. Forest plot showing multivariate logistic regression analysis of factors associated with diagnostic discordance between histopathology and immunohistochemistry. Lesion size >3 cm (OR: 2.84; 95% CI: 1.32-6.12; p=0.008) and extensive inflammation (OR: 3.21; 95% CI: 1.47-6.98; p=0.003) were identified as significant independent predictors. Error bars represent 95% confidence intervals. Factors with confidence intervals crossing the vertical line at OR=1.0 are not statistically significant.

Table 3. Multivariate analysis of factors associated with diagnostic discordance.

Factor	OR	95% CI	p-value
Lesion size >3 cm	2.84	1.32-6.12	0.008
Extensive inflammation	3.21	1.47-6.98	0.003
Keratocyst histology	2.10	0.89-4.82	0.042
Anterior location	1.45	0.68-3.09	0.337
Age >50 years	1.28	0.61-2.68	0.512
Male sex	1.15	0.56-2.37	0.704

OR: Odds Ratio; CI: Confidence Interval

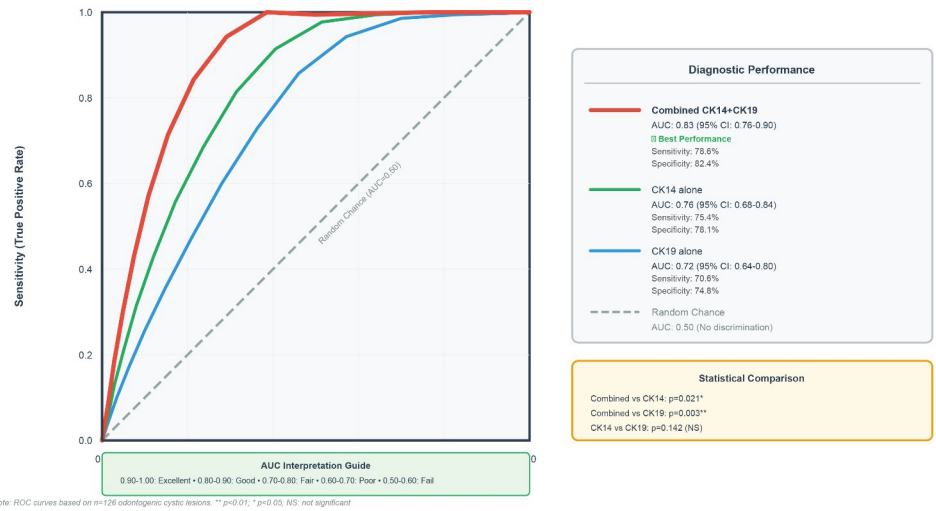

Figure 2. Receiver operating characteristic (ROC) curves comparing the diagnostic performance of individual markers (CK14 and CK19) versus combined marker analysis (CK14+CK19) for odontogenic cystic lesions. Combined CK14+CK19 analysis demonstrated superior performance with an AUC of 0.83 (95% CI: 0.76-0.90) compared to CK14 alone (AUC: 0.76) and CK19 alone (AUC: 0.72). The diagonal reference line represents random chance (AUC: 0.50).

Table 4. Diagnostic performance of immunohistochemical markers.

Marker	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	AUC (95% CI)
CK14 alone	89.7	65.2	75.4	78.2	81.5	0.76 (0.68-0.84)
CK19 alone	83.3	60.8	70.6	74.1	72.4	0.72 (0.63-0.81)
CK14+CK19	91.2	70.5	78.6	82.7	83.9	0.83 (0.76-0.90)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUC: Area Under the Curve.

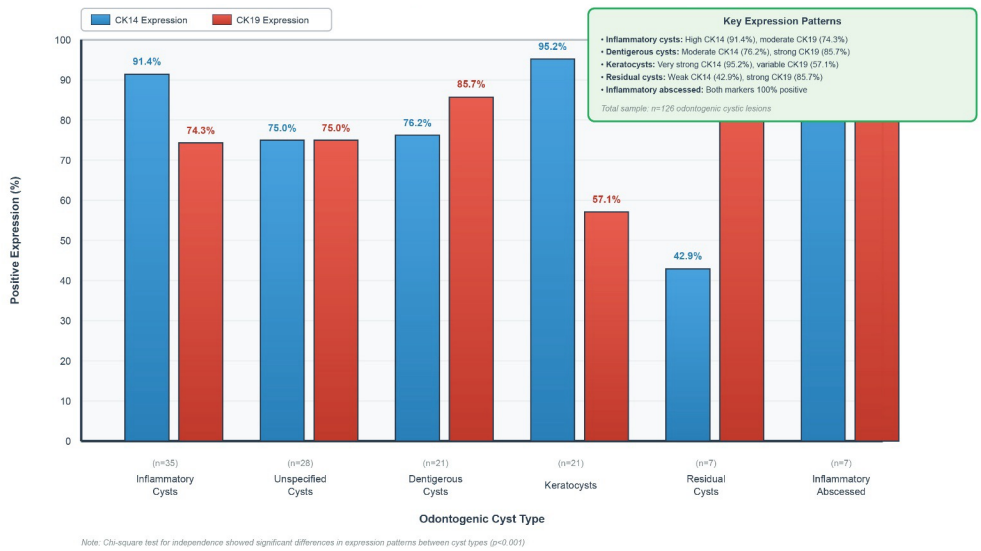

Figure 3. Bar graph showing the distribution of immunohistochemical expression patterns (CK14 and CK19) across different types of odontogenic cysts. Data are presented as percentages of positive cases within each diagnostic category. Inflammatory cysts showed high CK14 expression (91.4%) with moderate CK19 (74.3%). Dentigerous cysts demonstrated moderate CK14 (76.2%) but strong CK19 (85.7%). Keratocysts exhibited characteristic strong CK14 (95.2%) with variable CK19 (57.1%). Residual cysts displayed weak CK14 (42.9%) but strong CK19 (85.7%).

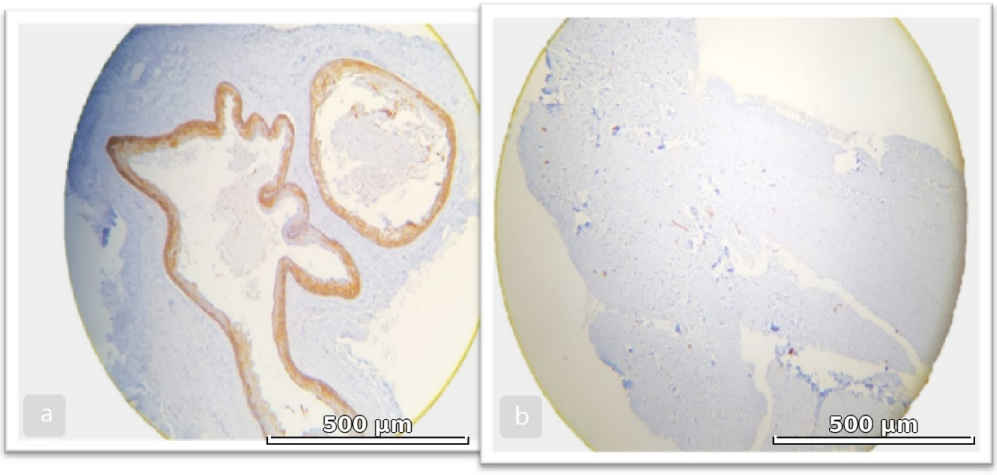

Figure 4. Representative photomicrographs of immunohistochemical staining patterns in odontogenic cysts (×200 magnification). (A) Keratocyst showing strong positive immunoreactivity for both CK14 and CK19 (double positive, ++/++). Brown staining indicates positive immunoreactivity; hematoxylin counterstain (blue) highlights cell nuclei. (B) Dentigerous cyst showing negative staining for both CK14 and CK19 (-/-), demonstrating absence of immunoreactivity for both markers. Scale bar = 500 µm.

DISCUSSION

This study represents one of the largest comprehensive analyses of diagnostic concordance between conventional histopathology and immunohistochemical examination using CK14 and CK19 markers in odontogenic cystic lesions from a Latin American population (1,2). The substantial agreement observed (κ=0.68) demonstrates that immunohistochemistry provides valuable complementary diagnostic information that can enhance the accuracy of conventional morphological assessment, particularly in diagnostically challenging cases (3,4).

The prevalence distribution of cystic lesions in our study aligns with previous reports from Latin American populations, where inflammatory cysts predominate due to the high prevalence of untreated dental caries and subsequent periapical pathology (5,6). Our finding that inflammatory cysts were most frequent (27.8%) is consistent with studies from Brazil, Chile, and Mexico, which report prevalence rates ranging from 25% to 40% for this lesion type (7,8). The slight female predominance (58.7%) observed in our cohort differs from some European studies that report male predominance, suggesting potential population-specific differences in disease distribution that warrant further investigation (9,10).

The mandibular preference (69.8%) observed in our study is consistent with the published literature and likely reflects the greater volume of odontogenic tissue and longer tooth roots in the posterior mandible, which provide more substrate for cyst development (11). Additionally, the posterior mandibular region has been associated with higher rates of impacted third molars, which are frequently involved in dentigerous cyst formation (12).

The high positive expression rates for both CK14 (89.7%) and CK19 (83.3%) confirm the epithelial origin of these lesions and support the utility of these markers in differential diagnosis (13,14). The variable expression patterns among different cyst types suggest that immunohistochemical profiling could assist in subtype classification, particularly when morphological features are ambiguous due to inflammation or sampling limitations (15). Our finding that keratocysts exhibited strong CK14 expression (95.2%) with

variable CK19 positivity (57.1%) is consistent with their recognized unique biological behavior and supports the WHO reclassification of these lesions as odontogenic keratocysts rather than keratocystic odontogenic tumors (16,17).

The improvement in diagnostic accuracy with combined CK14+CK19 analysis (κ=0.74 versus κ=0.68 for histopathology alone) supports the concept of multimarker approaches in diagnostic pathology (18,19). This 6.4% absolute improvement represents a moderate clinical gain that, while not dramatic, may have meaningful implications in selected diagnostic scenarios, particularly for keratocysts where misclassification carries distinct treatment implications (20). However, the clinical impact of this improvement should be interpreted cautiously, given the single-center design and the relatively small numbers in some subgroups. The combined marker approach was particularly valuable for keratocysts, which showed the highest discordance rate with conventional histopathology, likely reflecting their morphological heterogeneity and potential for misclassification as other developmental cysts (21).

The identification of lesion size >3 cm and extensive inflammation as independent predictors of diagnostic discordance provides valuable insights (22). Regarding the subgroups with lower concordance: keratocysts (66.7%) presented the greatest diagnostic challenge, likely because their characteristic palisaded basal cell layer and corrugated parakeratotic surface can be partially obscured when the cyst wall undergoes secondary inflammation. In these cases, IHC with CK14 (strong, >95% positivity) may serve as a valuable confirmatory tool. Similarly, residual and inflammatory abscessed cysts showed variable concordance, possibly because their epithelial lining undergoes reactive changes that mimic other cyst types morphologically. The completely unclassifiable 'undetermined cyst' category (n=7, 0% concordance with HP) showed 100% reclassification by IHC, which highlights the specific utility of immunohistochemistry as a tiebreaker in morphologically ambiguous cases. These findings suggest that IHC may be most cost-effective when ordered selectively for cases with these specific high-discordance features, rather than implemented routinely for all odontogenic cysts (23).

Several limitations should be acknowledged. First, this study was conducted at a single tertiary referral center, which may introduce selection bias toward more complex cases. Second, the relatively small numbers in some cyst categories (n=7 for residual, inflammatory abscessed, and undetermined cysts) limit the statistical power for subgroup analyses. Third, we did not include molecular markers or genetic analysis, which might provide additional diagnostic and prognostic information, particularly for keratocysts with their known association with PTCH1 mutations (24,25). Future multicenter studies with larger sample sizes and expanded marker panels are needed to validate and extend these findings.

CONCLUSIONS

This single-center prospective study demonstrates substantial diagnostic concordance (κ=0.68) between conventional histopathology and immunohistochemical analysis using CK14 and CK19 markers in odontogenic cystic lesions. The combined use of both markers may enhance diagnostic precision, particularly in cases with extensive inflammation or lesion size >3 cm, which were identified as independent predictors of discordance. Immunohistochemistry may be particularly useful as a complementary tool in morphologically challenging cases, especially keratocysts and undetermined cysts. However, given the single-center design and small sample sizes in some subgroups, multicenter validation is necessary before recommending standardized implementation of these protocols as routine diagnostic workup.

CLINICAL RELEVANCE

The findings of this study have direct implications for clinical practice in oral and maxillofacial pathology. First, the substantial concordance (72.2%) between conventional histopathology and immunohistochemistry validates the continued use of morphological assessment as the primary diagnostic approach for odontogenic cysts. However, the 27.8% discordance rate highlights the value of immunohistochemical markers as complementary tools, particularly in cases where morphological features are ambiguous or obscured by secondary changes.

Clinicians and pathologists should consider requesting CK14 and CK19 immunohistochemical studies in specific clinical scenarios: (1) lesions larger than 3 cm where architectural distortion may complicate morphological assessment; (2) specimens with extensive inflammatory infiltrate (>50%) that obscures epithelial characteristics; (3) cases where the differential diagnosis includes keratocyst, given its higher recurrence rate and need for more aggressive surgical management; and (4) situations where the initial histopathological diagnosis is uncertain or classified as "undetermined cyst."

The distinct immunohistochemical profiles identified for different cyst types provide practical diagnostic guidance. Strong CK14 with variable CK19 expression supports a keratocyst diagnosis, while moderate CK14 with strong CK19 favors dentigerous cyst. These patterns can help resolve diagnostic dilemmas and ensure appropriate treatment planning, ultimately improving patient outcomes through more accurate diagnosis and tailored therapeutic approaches.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest related to this study.

ETHICS: This study was approved by the Institutional Ethics Committee of Fundación Hospital Universitario Metropolitano (Protocol No. FHUM-2021-018) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for the use of their biological samples for research purposes.

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