ARTÍCULO ORIGINAL

Interobserver variability in the histopathological classification and grading of dysplasia in elevated colon lesions in the city of Lima

Variabilidad interobservador en la clasificación histopatológica y en la graduación de displasia de lesiones elevadas de colon en la ciudad de Lima

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ABSTRACT
Colonic polyp refers to lesions that exhibit a protrusion of the mucosa, regardless of histology. The most recent WHO classification is based on a better understanding of these lesions; however, its application in daily practice could be subject to interobserver variability biases that could have clinical implications. **Objectives:** To determine the interobserver variability in the histopathological reporting and grading of dysplasia of samples obtained from elevated colon lesions in a private laboratory in the city of Lima. **Materials and methods:** Observational, descriptive, and prospective study: Case series type. All biopsies of elevated colon lesions received over a period of 3 months were evaluated by two observers without clinical information of the cases, to diagnose the lesions according to the WHO classification. In cases of diagnostic differences, the cases were evaluated together to reach a consensus. **Results:** A Kappa coefficient value of 0.458 was obtained in the diagnostic classification of elevated colon lesions, while a Kappa value of 0.416 in the evaluation of dysplasia; indicating moderate agreement. **Conclusions:** Despite achieving moderate agreement between evaluators, this work demonstrates the importance of not only relying on morphological criteria for diagnostic classification, but also including criteria of location and size of these lesions to increase diagnostic accuracy.
Keywords: *Interobserver variability; Colonic polyps; Colonic diseases; Colonic neoplasms; Colonoscopy (source: MeSH NLM).*

RESUMEN
Pólipo colónico hace referencia a lesiones que presentan una protrusión de la mucosa, sin contar la histología. La clasificación más reciente de la OMS está basada en un mejor conocimiento de estas lesiones; sin embargo, su aplicación en la práctica diaria podría estar sujeta a sesgos de variabilidad interobservador que podrían tener implicancias clínicas. **Objetivos:** Determinar la variabilidad interobservador en el reporte histopatológico y la graduación de displasia de muestras obtenidas de lesiones elevadas de colon en laboratorio privado de la ciudad de Lima. **Materiales y métodos:** Estudio observacional, descriptivo y prospectivo: Tipo serie de caso. Todas las biopsias de lesiones elevadas de colon recibidas en un periodo de 3 meses fueron evaluadas por dos observadores sin información clínica de los casos, a fin de diagnosticar las lesiones de acuerdo con la clasificación de la OMS. En los casos de diferencias diagnósticos, los casos fueron evaluados en conjunto a fin de llegar a un consenso. **Resultados:** Se obtuvo un valor del coeficiente Kappa de 0,458 en la clasificación diagnostica de lesiones elevadas de colon, mientras que un valor de Kappa de 0,416 en la evaluación de displasia; indicando una concordancia moderada. **Conclusiones:** A pesar de lograr un acuerdo moderado entre los evaluadores, este trabajo demuestra la importancia de no solo recaer en criterios morfológicos para la clasificación diagnóstica; si no incluir criterios de localización y tamaño de estas lesiones para poder incrementar la precisión diagnóstica.
Palabras clave: *Variaciones dependientes del interobservador; Pólipos del colon; Enfermedades del colon; Neoplasias del colon; Colonoscopia (fuente: DeCS Bireme).*

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INTRODUCTION

Polyp is a clinical definition referring to elevated lesions protruding from the mucosa, regardless of their histological nature [1]. In the colon, polyps can be grouped into inflammatory, hamartomatous, hyperplastic, and neoplastic [2]. Previously, adenomatous polyps were considered neoplastic and hyperplastic polyps were considered non-neoplastic; however, over time it was observed that these carry a certain degree of malignancy potential, necessitating a new classification [3]. Currently, neoplastic polyps are generally grouped into serrated polyps and adenomatous polyps. Adenomatous polyps include tubular, villous, and tubulovillous types; while serrated polyps include hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas [4].

Regarding the prevalence of these serrated polyps in our country, the data appears to be like that of other regions of the world [5]. It should be noted that the same patient can have different types of serrated polyps [6].

Sessile serrated lesions represent approximately 20% of serrated polyps [7]. They are more frequently found in the right colon, and their progression to malignancy has been poorly studied, with reports suggesting it can occur within 1 year; however, it is still lower compared to adenoma progression [8]. Traditional serrated adenoma represents up to 3% of serrated polyps, with these being more common in the left colon [9]. Hyperplastic polyp is the most common type of serrated polyp, accounting for 80% of them [10]. They are usually found in the distal colon and rectum, and there are two subtypes: microvesicular and rich in goblet cells [11].

One of the main causes of the development of colorectal cancer is the presence of colorectal polyps. In our country, colorectal cancer ranked fourth in terms of incidence in 2018, with an adjusted mortality rate of 6.4 deaths per 100,000 inhabitants in 2016, making it a public health problem in the Peruvian population [12]. Regarding their relationship with the development of colorectal cancer, adenomatous polyps are the ones that have been scientifically most associated with it [13]. However, a study has shown that serrated polyps are also associated with the development of colorectal cancer [14,15], which previously had no known association.

Classification by the WHO

The World Health Organization (WHO) in 2019 presented the fifth edition of the classification of tumors of the digestive system, which recognizes 4 subtypes of serrated polyps, including hyperplastic polyps (HPs), sessile serrated lesions (SSLs), sessile serrated lesions with dysplasia (SSLsD), and traditional serrated adenomas (TSAs) [16]. It is worth noting that if the morphology of the lesion does not correspond to any of the mentioned serrated polyps, it is called unclassified serrated adenoma.

Sessile serrated lesions for diagnosis require the unequivocal presence of at least one crypt with architecturally distorted serration, which includes horizontal growth of the crypt along the muscularis mucosa, dilatation of the crypt base, serrated morphology along the crypt, or asymmetric proliferation of the crypt [17].

Traditional serrated adenoma is characterized by typically eosinophilic cells with elongated nuclei, serration morphology in the form of a cleft, and ectopic crypt foci [18]. Hyperplastic polyp has two subtypes, microvesicular HP and goblet cell HP. Histologically, it is characterized by serrated morphology in the upper two-thirds of the crypt with a funnel appearance and absence of abnormalities at the base. In goblet cell HP, most cells on the surface and crypt epithelium are goblet cells with small, uniform, basal nuclei. Crypts may show branching or be tortuous [18,19].

This study focus on studying the interobserver variability that exists when evaluating colon polyp biopsies in a pathology laboratory in Lima, Peru. Currently, there have been no interobserver variability studies in our country that evaluate colorectal polyps according to the latest WHO classification (2019). This research is relevant considering that, according to the new WHO classification, lesions previously classified as benign would require closer follow-up. Additionally, it is important to recognize the main characteristics that determine variability in histopathological diagnosis and degree of dysplasia, to provide relevant information for pathologists to optimize their diagnostic assessment.

MATERIALS AND METHODS

The study is an observational, descriptive, and prospective case series conducted at the Unilabs Pathology - Arias-Stella Institute of Pathology and Molecular Biology in Lima, Peru. It spanned from October 1st, 2021, to January 1st, 2022, involving 567 biopsies of elevated colon lesions. The target population included patients from Lima, Peru, whose biopsies met inclusion criteria.

Inclusion criteria included hyperplastic polyps, tubular adenomas, tubulovillous adenomas, villous adenomas, sessile serrated lesions, traditional serrated adenomas, unclassified serrated adenomas.

The exclusion criteria included Inflammatory pseudopolyps, cancers, non-epithelial lesions, lymphoid nodular hyperplasias, and other types of lesions that present as elevated colon lesions and do not meet the inclusion criteria.

The study focused on qualitative independent variables such as dysplasia classification and histopathological diagnosis according to WHO guidelines, and consensus degree as quantitative variables.

Once the database with the slides of elevated colon lesions was obtained, each slide was checked to ensure it contained only a single histopathological diagnosis, thus excluding from the sample those slides that presented more than one diagnosis. The final sample consisted of 567 slides.

Two specialists in anatomical pathology with 20 years of experience and working in the same center performed evaluations using convenience sampling.

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Before starting the study, the two evaluators met and jointly reviewed the diagnostic criteria of the WHO [17] for elevated colon lesions, as well as the operational definitions of variables. Each observer completed the data collection form on the classification and grading of dysplasia independently. Upon completing the data collection period, once it was verified that the number of cases evaluated allowed for statistically relevant conclusions, the slides from cases where there was disagreement between the two observers were separated, and they met to re-evaluate each case under a multi-headed microscope to establish a diagnostic consensus, which was then recorded in the database.

Analysis plan

Descriptive Statistics: Using the Kappa coefficient (κ) resulting from the agreement between two pathologists. If there is no agreement in any biopsy, both pathologists will evaluate the sample together to reach a consensus. For the interpretation of the Kappa coefficient (κ), the cutoff values used in this study were:

- κ = 0.21-0.40: Reasonable agreement.
- κ = 0.41-0.60: Moderate agreement.
- κ = 0.61-0.80: Substantial agreement.
- κ = 0.81-1.00: Almost perfect concordance.

Inferential statistics: The data were analyzed using Stata software version 17, and a p-value less than 0.05 was considered statistically significant.

Ethical considerations

This research work was submitted to the ethics committee of the Universidad Peruana Cayetano Heredia prior to its execution. No personal information of patients that could identify them was collected.

RESULTS

Study population description

According to the sample collection period initiated on October 1st, 2021, until January 1st, 2022, a total of 567 eligible slides were obtained based on the inclusion criteria outlined in the study.

Table 1. Histopathological classification results and dysplasia grading by both observers.

Diagnosis	Observer 1		Observer 2	
	n	%	n	%
Hyperplastic polyp	164	28.92	127	22.40
Sessile serrated lesion	85	14.99	34	6.00
Traditional serrated adenoma	7	1.23	6	1.06
Tubular adenoma	246	43.39	323	56.97
Villous adenoma	24	4.23	10	1.76
Tubulovillous adenoma	25	4.41	55	9.70
Unclassified serrated adenoma	16	2.83	12	2.11
Total	567	100.00	567	100.00

Observer 1 results:

Out of the 567 slides evaluated by Observer 1, 164 slides (28.92%) were classified as hyperplastic polyps, 85 (14.99%) as sessile serrated lesions, 7 (1.23%) corresponded to traditional serrated adenomas, 246 (43.39%) as tubular adenomas, 24 (4.23%) as villous adenomas, 25 (4.41%) as tubulovillous adenomas, and finally, 16 (2.82%) were classified as unclassified serrated adenomas (Table 1).

Additionally, the degree of dysplasia was determined in tubular, villous, and tubulovillous adenomas. 285 slides (96.61%) were classified as low-grade, and 10 (3.39%) as high-grade, totaling 295 (100%) (Table 2). On the other hand, in sessile serrated lesions and traditional serrated adenomas, 16 cases (17.39%) showed dysplasia and 76 cases (82.61%) did not show dysplasia, out of a total of 92 cases (100%) (Table 3).

Observer 2 results:

Out of the 567 slides evaluated by Observer 2, 127 slides (22.4%) were classified as hyperplastic polyps, 34 (6%) as sessile serrated lesions, 6 (1.06%) corresponded to traditional serrated adenomas, 323 (56.97%) as tubular adenomas, 10 (1.76%) as villous adenomas, 55 (9.7%) as tubulovillous adenomas, and finally, 12 (2.12%) were classified as unclassified serrated adenomas (Table 1).

Table 2. Dysplasia grading results of tubular, villous, and tubulovillous adenomas by both observers.

Dysplasia	Observer 1		Observer 2	
	n	%	n	%
Low grade	285	96.61	375	96.65
High grade	10	3.39	13	3.35
Total	295	100.00	388	100.00

Table 3. Results of dysplasia presence in sessile serrated lesions and traditional serrated adenomas by both observers.

Dysplasia	Observer 1		Observer 2	
	n	%	n	%
Present dysplasia	16	17.39	4	10.00
No dysplasia	76	82.61	36	90.00
Total	92	100.00	40	100.00

Table 4. Histopathological classification results with respect to anatomical location.

Diagnosis	Ascending colon		Transverse colon		Descending colon		Sigmoid colon		Total	
	n	%	n	%	n	%	n	%	n	%
Hyperplastic polyp	20	3.53	28	4.93	27	4.76	83	14.65	158	27.87
Sessile serrated lesion	28	4.94	7	1.23	5	0.88	18	3.18	58	10.23
Traditional serrated adenoma	5	0.87	2	0.36	0	0.00	0	0.00	7	1.23
Tubular adenoma	90	15.86	44	7.77	48	8.48	94	16.58	276	48.69
Villous adenoma	3	0.52	0	0	0	0.00	4	0.71	7	1.23
Tubulovillous adenoma	15	2.64	5	0.89	0	0.00	26	4.59	46	8.12
Unclassified serrated adenoma	6	1.05	1	0.18	2	0.35	6	1.05	15	2.63
Total	167	29.41	87	15.36	82	14.47	231	40.76	567	100.00

Similarly, in tubular, villous, and tubulovillous adenomas, 375 slides (96.65%) were classified as low-grade dysplasia, and 13 (3.35%) as high-grade dysplasia, out of a total of 388 cases (100%) (Table 2); while in sessile serrated lesions and traditional serrated adenomas, 4 cases (10%) showed dysplasia and 36 cases (90%) did not show dysplasia, out of a total of 40 cases (100%) (Table 3).

Colon location data results

Regarding location data, hyperplastic polyps were most found in the sigmoid colon (14.64%) and least frequently in the ascending colon (3.53%). Sessile serrated lesions were more frequent in the ascending colon (4.94%) and less frequent in the descending colon (0.88%). Tubular adenomas had a percentage of 16.58% in the sigmoid colon location, with the transverse colon (7.76%) being the least frequent location. Villous adenomas were not found in slides from the transverse or descending colon. They were found in the sigmoid colon (0.71%) and ascending colon (0.52%). Tubulovillous adenomas were most frequently found in the sigmoid colon (4.59%). Finally, unclassified serrated adenomas were found in equal percentages (1.05%) in both the ascending and sigmoid colon (Table 4).

Inferential statistics

A Kappa coefficient value of 0.458 was obtained in the evaluation of diagnoses of elevated colon lesions, with an agreement percentage of 63.49% and a 95% confidence interval of (0.45-0.46). In the evaluation of dysplasia, a Kappa value of 0.416 was found with a 95% confidence interval (0.36-0.48) (Table 5).

These Kappa values indicate moderate agreement

On the other hand, a Kappa coefficient value of -0.105 was obtained in the evaluation of diagnoses by both observers between hyperplastic polyps and sessile serrated lesions, with an agreement percentage of 49.79% and a 95% confidence interval of (-0.213 to 0.002) (Table 6).

These Kappa values do not indicate agreement

DISCUSSION

In any procedure, there is a certain degree of intrinsic error, especially when subjective assessment is the main

Table 5. Kappa coefficient results of histopathological classification and dysplasia grading.

Variable	Relationship	Kappa coefficient	Standard error	Agreement percentage	IC95%
Diagnosis	Obs 1 / Obs 2	0.458	0.002	63.49	0.45-0.46
	Obs 1 / Consensus	0.167	0.031	32.52	0.11-0.23
	Obs 2 / Consensus	0.29	0.033	45.63	0.23-0.35
Degree of dysplasia	Obs 1 / Obs 2	0.416	0.031	67.55	0.36-0.48
	Obs 1 / Consensus	0.168	0.044	41.08	0.08-0.25
	Obs 2 / Consensus	0.169	0.042	49.19	0.09-0.25

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Table 6. Kappa coefficient results of histopathological classification and dysplasia grading.

Variable	Relationship	Kappa coefficient	Standard error	Agreement percentage	IC95%
Diagnosis between hyperplastic polyp and sessile serrated lesion	Obs 1 / Obs 2	-0.105	0.055	49.79	-0.213-0.002

component of measurement. Errors can rarely be eliminated; however, knowledge of their origin, causes, and quantitative evaluations can decisively contribute to improving the quality of practice.

There are various ways to measure variability, and in the present study, interobserver variability was determined using the Kappa index because the variables considered are nominal [20].

It is worth mentioning that the Kappa index has limitations when interpreting its results. One limitation is due to the prevalence of the anomaly, whether the prevalence is low or high, it will result in an underestimated Kappa index. An additional limitation is the increase in categories, which is associated with decreased Kappa values [21].

In the literature search, no similar studies were found in our country comparing interobserver variability in elevated colon lesions. However, a study conducted in the United States compared the reproducibility of diagnosis entre hyperplasic polyp and Sessile serrated lesion using three proposed criteria, which are morphology, location, and size of the polyp. Since sessile serrated lesions and hyperplastic polyps can have overlapping morphologies, relying solely on morphological diagnosis leads to a higher degree of error. The use of these three criteria (morphology, location, and size) yielded a Kappa index of 0.88 (almost perfect agreement) [22]. A result highly comparable to that found in our study, where we obtained a kappa of -0.105, 95% CI (-0.213 to 0.002), based solely on the WHO morphological criteria for classification (Table 6).

This leads to a serious error in clinical practice, as there is known risk of progression from a sessile serrated lesion to colorectal cancer, unlike the benign diagnosis of a hyperplastic polyp.

Our criteria were based on the 2019 WHO classification, which does not include important characteristics such as polyp location and size [17]. It is important to introduce these criteria for better agreement between evaluators and to avoid diagnostic errors.

Additionally, since the processing of the sample influences the observation under the microscope of the crypt configuration, a study compared the inter-observer variability of two different methods of processing slides. The modified method, which involved flattening the sample before immersion in formalin, showed a higher percentage of agreement than the conventional method [23]. Specifications regarding the steps of the modified processing can be found in the following bibliography [24].

Similarly, in this project, we sought to find interobserver variability in dysplasia grading, finding a Kappa index of 0.416 (moderate agreement) (Table 5). A similar result was found in a study that evaluated interobserver agreement among five pathologists and dysplasia grading with a Kappa index of 0.415 (moderate agreement), where they based their assessment on nuclear pseudostratification, mitotic activity, nuclear polarity, nuclear pleomorphism, nucleoli, and nuclear shape.

The lowest agreement for dysplasia grading was observed in the assessment of nuclear shape, nucleoli, and mitotic activity [25].

It is worth noting that in our study, we had the participation of two pathologists, who were selected based on their years of experience (20 years) and currently working in the same laboratory.

In conclusion, despite achieving a moderate level of agreement between evaluators in determining interobserver variability and grading dysplasia in elevated colon lesions, it seems that relying solely on morphological criteria leads to a lower degree of agreement between evaluators. A study would be needed in our environment where the location, size, and processing method of each polyp sample are also compared to improve diagnostic accuracy. This way, the current diagnostic criteria can be updated.

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