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Accuracy of histologic inflammation scores in active ulcerative colitis: Dependence on biopsy sampling density

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INTRODUCTION

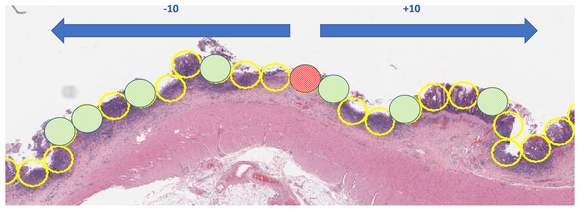
- Histological evaluation of colonic mucosal biopsies in patients with ulcerative colitis (UC) is a potentially informative adjunct to endoscopic evaluation in assessing disease activity in the clinical trial setting.
- Validated indices to grade inflammation, such as the Geboes, Nancy and Robarts indices, are based on pathological grading of individual inflammatory changes such as mononuclear and granulocytic infiltration and ulceration.
- Although mucosal inflammation in UC is characteristically uniform on the endoscopic scale, the histological changes are distributed non-uniformly on the microscopic scale of individual biopsies, imposing biopsy sampling error of uncertain magnitude.

AIM

The aim of the present study was to utilize statistical modeling to calculate the accuracy of histological inflammation scores in localized regions of mucosa as a function of sampling density and to determine the densities needed to achieve a specified accuracy for biopsy-based histological grading.

METHODS

Colectomy specimens of 11 consecutive patients with severe pan-UC were sectioned for histology. A randomly selected slide from the left and right side of each specimen was digitally scanned at 40X and the mucosal image was segmented into consecutive 1 mm-diameter fields to simulate biopsies. The patients comprised 7 males and 4 females, median age 29 y. Ten to 67 fields were scored per slide (median 44, IQR= [33,61]) for a total 995 fields. Inflammation in each field was scored jointly by two gastrointestinal pathologists using the Geboes subscores [2] and the Nancy (NHI) and Robarts histological indices (RHI) [3,4]. The influence of sampling density on accuracy within a 2 cm target was determined based on agreement statistics between the mean score of k randomly sampled fields with k varying from 1-10, within a series of ±10 consecutive fields, and the series mean via 2500 iterations.



For each slide (mean 45 mm) (A)

1. Consecutive 1 mm fields (virtual biopsies) are scored by two pathologists
2. Select 1 field at random and a window of 10 fields on either side
3. Reference score (Sr) = mean histologic score of 21 fields
4. Select k-1 fields at random
5. Determine mean score of k biopsies (Sk)
6. Generate agreement statistics (Sr vs. Sk)
7. Repeat steps 4 and 5 2500 times
8. Use bootstrap to obtain mean, 95% CI
9. Repeat steps 2 through 8 for k=1,2,…,10

Table 1. Study population descriptive statistics

	Mean	SE	95%CI
Nancy Histologic Index	2.67	0.15	2.36, 2.99
Robarts Histologic Index	14.92	1.30	12.20, 17.65
Chronic Inflammation	1.97	0.12	1.71, 2.22
Lamina Propria Neutrophils	1.56	0.14	1.27, 1.85
Intraepithelial Neutrophils	1.56	0.16	1.22, 1.91
Erosions or Ulcers	1.03	0.14	0.74, 1.31

Table 2a. Intraclass correlation coefficients and error tolerance statistics for NHI and RHI by biopsy density

	Nancy Histologic Index (range 0-5)						Robarts Histologic Index (range 0-33)					
Biopsy density	ICC	95% CI		Error	95% CI		ICC	95% CI		Error	95% CI	
1	0.73	0.48	0.87	0.40	0.25	0.66	0.76	0.56	0.86	3.20	2.08	5.36
2	0.84	0.66	0.93	0.28	0.18	0.48	0.86	0.72	0.93	2.30	1.38	3.87
3	0.89	0.75	0.95	0.22	0.14	0.39	0.90	0.80	0.95	1.87	1.19	3.25
4	0.92	0.83	0.96	0.19	0.12	0.33	0.93	0.85	0.97	1.56	0.97	2.66
5	0.94	0.86	0.97	0.16	0.10	0.29	0.94	0.89	0.97	1.35	0.86	2.44

Table 2b. Interclass correlations coefficients for Geboes subscores by biopsy density

	Chronic inflammation			Lamina propria neutrophils			Intraepithelial neutrophils			Erosions or ulcers		
Biopsy density	ICC	95% CI		ICC	95% CI		ICC	95% CI		ICC	95% CI	
1	0.72	0.48	0.85	0.82	0.65	0.91	0.65	0.41	0.79	0.64	0.36	0.82
2	0.83	0.63	0.92	0.90	0.80	0.95	0.78	0.58	0.89	0.78	0.52	0.89
3	0.88	0.72	0.94	0.93	0.86	0.97	0.85	0.70	0.92	0.84	0.64	0.93
4	0.91	0.78	0.96	0.95	0.90	0.98	0.89	0.78	0.95	0.88	0.71	0.95
5	0.93	0.84	0.97	0.96	0.92	0.98	0.91	0.82	0.96	0.91	0.77	0.96

Figure 2a. Average gain in average ICC per additional biopsy. (Left) Change in ICC with increasing biopsy density for Nancy and Robarts indices and Geboes subscores.

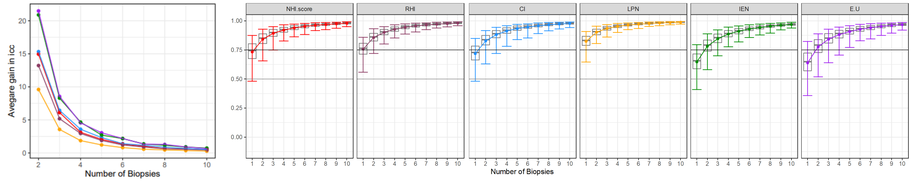
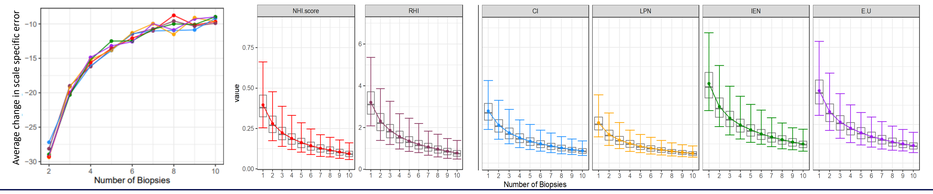


Figure 2b. Average change in scale specific error per additional biopsy. Change in error with increasing biopsy density for indices and individual histologic components.



NHI = Nancy Histologic Index
RHI = Robarts Histologic Index
CI = Chronic inflammation
LPN = Lamina propria neutrophils
IEN = Intraepithelial neutrophils
EU = Erosions or ulcers

Figure 3. ICC and scale specific error in areas of high and low inflammation

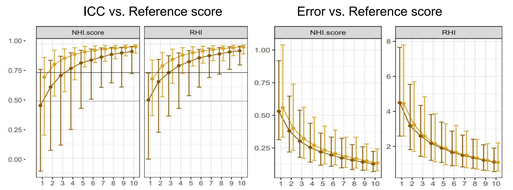
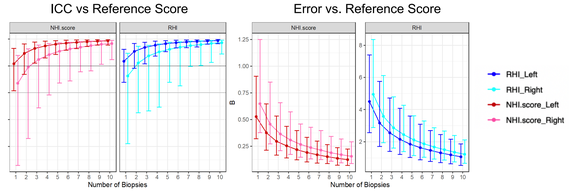


Figure 4. ICC and scale specific error in right vs. left sided biopsies



CONCLUSIONS

- Using statistical modeling we show that the accuracy of histological grading improves across all indices as the biopsy density increases, the largest proportional gains occurring with the addition of the second and third biopsies but diminishing thereafter.
- One biopsy can achieve moderate to good accuracy (mean interclass correlation coefficients [ICC] of 0.73 95% CI (0.48-0.87) with the Nancy histologic index and 0.76 95% CI (0.56-0.86) with the Robarts histologic index), whereas sampling three biopsies results in a large proportional gain in achieving good accuracy (ICC ≥ 0.75) with 95% confidence.
- Our results provide a set of benchmarks and guidance for the design and interpretation of clinical trials using biopsies to assess inflammation in UC.

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