Digestive and Liver Disease 51 (2019) 812–817

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Correlation between endoscopic and histological validated scoring indices in Crohn's disease

Wenbin Gong[a,1], Kun Guo[b,1], Tao Zheng[b], Miao Fang[c], Haohao Xie[c], Weijie Li[c], Zhiwu Hong[b], Huajian Ren[b], Guosheng Gu[b], Gefei Wang[b], Xiuwen Wu[b], Zhiming Wang[b,*], Jianan Ren[b,*], Jieshou Li[b]

[a] School of Medicine, Southeast University, Department of General Surgery, Jinling Hospital, PR China
[b] Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, PR China
[c] Department of General Surgery, Jinling Hospital, Nanjing Medical University, PR China

ARTICLE INFO

Article history:
Received 26 November 2018
Accepted 6 January 2019
Available online 22 January 2019

Keywords:
Crohn's disease
GHAS
Histological remission
NCS
SES-CD

ABSTRACT

Background: It is of crucial importance to evaluate disease activity by means of endoscopy and histopathology in Crohn's disease (CD). Nonetheless, correlation between endoscopic and histological validated indices has not been verified.
Aims: We aim to correlate the Simple Endoscopic Score for Crohns disease (SES-CD) with two validated widely used histological indices in patients with established CD.
Methods: The SES-CD at the worst affected area was scored and histological disease activity using Global Histologic Disease Activity Score (GHAS or D'Haens score) and the Naini and Cortina Score (NCS) was scored independently by two pathologists blinded to the clinical information and endoscopic results. Spearman correlation between the SES-CD, GHAS and NCS were performed.
Results: 143 patients, 32 with SES-CD scores 0–2, 57 with 3–6, 37 with 7–15, and 17 with ≥16. Correlation coefficients between SES-CD and GHAS were r = 0.86 (95% CI 0.80–0.91, p < 0.001) and between SES-CD and NCS r = 0.85 (95% CI 0.81–0.88, p < 0.001). There was a strong correlation between the two histological indices (r = 0.70, 95% CI 0.59–0.78, p < 0.001). Mucosal healing without histological disease activity was most correlated with SES-CD score 0 or 1.
Conclusions: The SES-CD strongly correlates with both GHAS and NCS. The SES-CD of 0 to 1 best represents histological remission that correlates with quiescent disease activity.

1. Introduction

Crohn's disease (CD) is a chronic, transmural inflammatory disorder that can involve any part of the gastrointestinal tract with unknown etiology [1,2]. There is growing evidence that mucosal healing may ameliorate the natural course of inflammatory bowel disease (IBD) [3]. Mucosal healing is always associated with the reduced need for surgery, hospitalization rates and relapse rates, and has emerged as the major therapeutic goal in CD [3–5]. At present, there is no acknowledged criterion for endoscopic mucosal healing while most studies define mucosal healing as absence of mucosal ulceration at endoscopy [6–9]. Traditional clinical indices in CD, such as the Harvey Bradshaw index (HBI) and the Crohn's disease activity index (CDAI), are not completely correlated with endoscopic activity [10,11]. Furthermore, the presence of endoscopic mucosal healing does not necessarily reflect the absence of histologic inflammation or to say quiescent microscopic disease, as up to one-third of biopsies from CD patients with endoscopically healed mucosa can display evidence of persistent histologic inflammation [12,13]. The relationship between endoscopy and histology for CD patients has not been investigated completely [14]. It is still ambiguous how well they correlate and whether consistency between endoscopy and histology reflects more reliable disease activity than using each method alone.

The Simple Endoscopic Score for Crohn's disease (SES-CD), a simple endoscopic activity score developed in order to simplify the Crohn's disease Endoscopic Index of Severity (CDEIS) [15], is currently one validated endoscopic index for evaluation of CD and demonstrated to be more efficient than the CDEIS [16,17]. The SES-CD has been prospectively validated and has high intra-rater and inter-rater reproducibility [15,18–20]. Furthermore, the SES-CD is

* Corresponding authors. Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, PR China.
E-mail addresses: wzmdoc@163.com (Z. Wang), jiananr@gmail.com (J. Ren).
[1] Wenbin Gong and Kun Guo contributed equally to this work.

https://doi.org/10.1016/j.dld.2019.01.010
1590-8658/

highly correlated with the CDEIS [15,21] and has a good strength in both clinical trials and practices [22].

The numerical histological scoring instruments, Global Histologic Disease Activity Score (GHAS or D'Haens score) and the Naini and Cortina Score (NCS), are widely used at present with capability of grading both ileal and colonic specimens separately [23,24]. The GHAS consists of 8 items, with a total score from 1 (no activity) to 13 (severe disease activity). And a score of 4 or lower indicates remission, whereas a score more than 10 indicates severe disease [23]. The NCS, with low inter-observer variability (correlation coefficient, 0.94–0.96), consists of 15 items and admits to separately score of the ileum (5 items) and colon (10 items). It has a scale of 0–10 for ileum and 0–17 for colon [24].

At present, correlation between endoscopic and histological validated indices in CD has not been fully examined. Therefore, the primary aim of this study is to correlate the SES-CD with two validated histological assessment of disease severity (GHAS and NCS) in patients with established CD. The secondary aim is to determine whether the SES-CD of 0–2 best represents remission, on account of the hypothesis that actual mucosal healing should adequately correlate with quiescent histopathology.

2. Materials and methods

2.1. Study design

Between July 2016 and June 2018, a single centre cohort of patients with established CD were enrolled, who had been diagnosed on the basis of standard criteria [25] in our medical institution, a referral tertiary teaching hospital. Patients with CD who evaluated with ileocolonoscopy by a single endoscopist were included, whereas patients would be excluded if they had ulcerative colitis (UC), upper gastrointestinal CD, perianal disease, obvious fibrous stenosis with obstructive symptoms, enteric infection and/or cancer. Study subjects were recruited regardless of their clinical disease activity. The institutional review board at Jinling Hospital approved this study and waived informed consent as this was a retrospective review.

2.2. Endoscopy

Ileocolonoscopy was performed by a single endoscopist that experienced in inflammatory bowel disease and the SES-CD score (Table S1) in the worst affected area was assessed. The endoscopist was blinded to the clinical disease severity, and some patients would have multiple biopsies taken from both ileum and colon by a single endoscopy if necessary. Endoscopy reports were reviewed from electronic medical records between July 2016 and June 2018. Only patients with complete ileocolonoscopic examinations were included, and they would be excluded if a SES-CD score was not recorded at the time of endoscopy or if biopsies were not taken for histopathological examination. For the assessment of endoscopy finds with SES-CD, the intestine was divided into terminal ileum, right, transverse, and left colon, and rectum. And the sum of all variables from these 5 segments was scored. In particular, the SES-CD score $\leq$2 was defined as endoscopic remission, 3–6 mild activity, 7–15 moderate activity, and $\geq$16 severe active disease [26,27]. The data of subjects, including age, gender, procedure date, lesion region and SES-CD score, were collected at time of endoscopy. However, none of the patients' name, date of birth, work unit or home address was documented in order to safeguard patient privacy.

2.3. Histopathology

The Global Histologic Disease Activity Score (GHAS, Table S2) and the Naini and Cortina Score (NCS, Table S3), were scored independently by two gastrointestinal histopathology specialists that blinded to clinical information and endoscopic results of the subjects. For the GHAS, eight histological components were assessed independently and summed including epithelial damage, architectural changes, infiltration of mononuclear cells in the lamina propria, polymorphonuclear cells in the lamina propria and epithelium, erosions/ulcers, granulomas, and the number of biopsy specimens affected. "Moderate increase" corresponded to twice the number of cells that could normally be expected, and "severe increase" up to more than twice the normal number of cells. The GHAS score ranged from 1 to 16 with 1 indicative of the absence of significant histological disease and 16 indicating severely active disease; histological remission corresponded to a GHAS score $\leq$4. By contrast, the NCS consisted of 15 histological components that allowed for separate evaluating of the ileum (5 components) and colon (10 components) as shown in Table S-3. The NCS score ranging from 0 to 27 (0 to 10 for ileum and 0 to 17 for colon), with 0 indicating the absence of histological disease and 27 indicative of severe disease activity.

Table 1
Demographic characteristics of patients with CD.

Characteristics	Patients, no. (%)
Age, mean (SD), y	33.4 (12.5)
Sex	
Male	89 (62.2)
Female	54 (37.8)
Lesion distribution	
Ileum	68 (47.6)
Colon	47 (32.9)
Both ileum and colon	28 (19.6)
Number of biopsies taken per patient	
1	6 (4.2)
2	22 (15.4)
3	41 (28.7)
4	37 (25.9)
5	24 (16.8)
6	13 (9.1)

2.4. Statistical analysis

The patient demographics, distribution of SES-CD and histological scoring indices were presented by descriptive statistics, bar diagram and scatterplots. The spearman correlation analysis between SES-CD, GHAS and NCS score was performed and the confidence intervals were acquired by method of bootstrapping. A correlation coefficient (r) of +1 or −1 shows a completely linear relationship between two continuous variables, whereas a correlation coefficient of 0 indicates no linear relationship. Specifically, the absolute value of r from 0 to 0.19 is considered to be a very weak correlation, 0.2 to 0.39 be weak, 0.4 to 0.59 be moderate, 0.6 to 0.79 be strong, and 0.8 to 1.0 be a very strong correlation [28]. P value < 0.05 was considered statistically significant, and all tests were 2-sided. Statistical analyses were performed using SPSS PASW Statistics software, version 20.0.

3. Results

3.1. Patients characteristics

A total of 149 CD patients were investigated. Six patients were excluded due to the inconsistent histological assessment score between the two histopathologists. Consequently, 143 patients were eligible to the final analysis, with the mean age of 33.4 years (SD = 12.5 years) and 89 (62.2%) patients were male. The demographic characteristics were listed in Table 1.

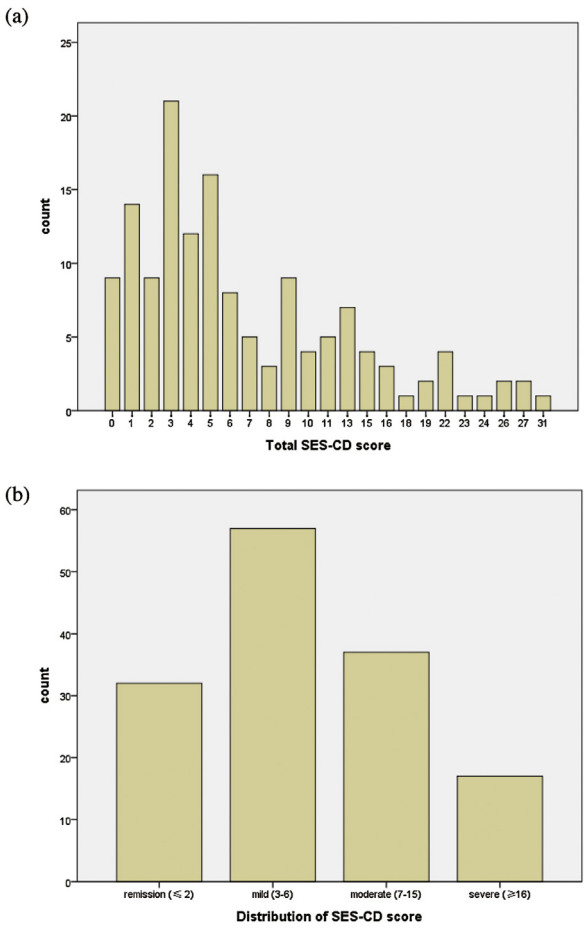

Fig. 1. (a) The total SES-CD score and (b) the grade distribution of SES-CD score for the patients with CD.

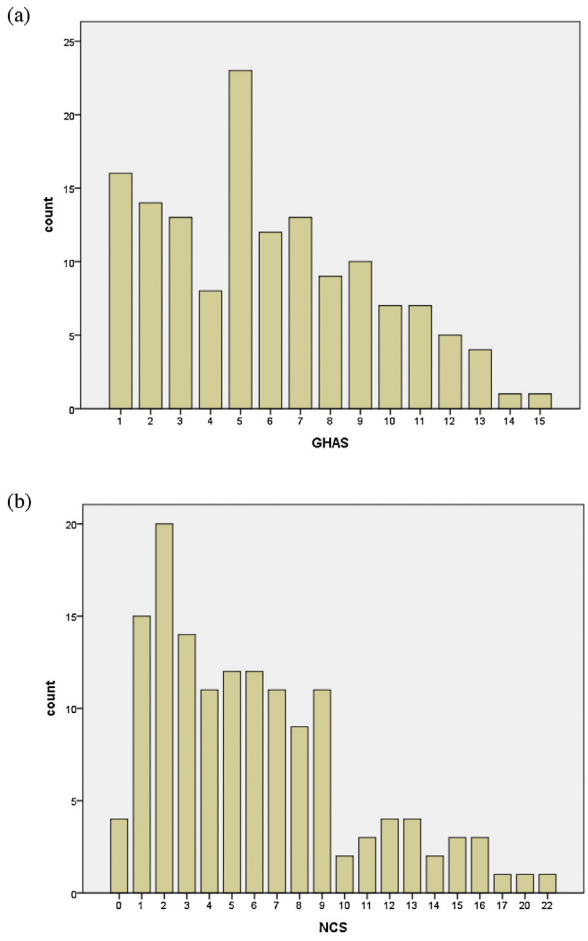

Fig. 2. (a) The GHAS score and (b) the NCS score of the patients with CD.

3.2. Endoscopy

Almost all levels of the SES-CD were represented, ranging from 0 to 31 with a median SES-CD score 5 and interquartile range 3–10 (Fig. 1(a)). Besides, the SES-CD score has been divided into 4 grades to correlate with clinical activity as described above: SES-CD score 0–2 (remission), 3–6 (mild activity), 7–15 (moderate activity), and ≥16 (severe active disease). In general, 32/143 (22.4%) patients had a remission, 57/143 (39.9%) mild, 37/143 (25.9%) moderate and 17/143 (11.9%) had severe disease activity (Fig. 1(b)).

3.3. Histopathology

The distribution of GHAS score was shown as Fig. 2(a), ranging from 1 to 15, with the median 5 and interquartile range 3–8. Overall, 51/143 (35.7%) patients had a remission and 18/143 (12.6%) had severely active disease. The distribution of NCS score was represented as Fig. 2(b), which ranged from 0 to 22 with a median NCS score 5 and interquartile range 2–8.

3.4. Correlation between endoscopic and histological scores

The correlation coefficient (r) and confidence intervals (CI) between the SES-CD and GHAS was r = 0.86 (95% CI 0.80–0.91, $p < 0.001$), and between the SES-CD and NCS was r = 0.85 (95% CI 0.81–0.88, $p < 0.001$). These correlations were classified as very strong in consideration of r > 0.8. Moreover, the GHAS and NCS histological indices had a strong correlation: r = 0.70 (95% CI 0.59–0.78, $p < 0.001$). All correlations between the SES-CD, GHAS and NCS were statistically significant with $p < 0.001$ (Fig. 3).

Furthermore, the correlations analysis of ileal and colonic CD were performed respectively. For the ileitis of CD, the correlations between the SES-CD, GHAS and NCS were very strong, with the correlation coefficient between the SES-CD and GHAS 0.83 (95% CI 0.73–0.90, $p < 0.001$) and between the SES-CD and NCS 0.81 (95% CI 0.71–0.88, $p < 0.001$) (Fig. 4). In contrast, the correlations for colitis of CD were slightly weaker, with the correlation coefficient between the SES-CD and GHAS 0.74 (95% CI 0.53–0.87, $p < 0.001$) and between the SES-CD and NCS 0.62 (95% CI 0.41–0.78, $p < 0.001$) (Fig. 5).

3.5. SES-CD level for histological remission

To investigate that whether SES-CD ≤2 best represents the real remission, they were assessed against the histological remission (GHAS score from 1 to 4). There were 9 patients with a SES-CD = 0, 14 with SES-CD = 1 and 9 with SES-CD = 2. Among them, 6/9 (66.7%) patients with a SES-CD = 0 had a GHAS = 1, 7/14 (50.0%) patients with a SES-CD = 1 and 2/9 (22.2%) patients with a SES-CD = 2. The odds ratio (OR) between SES-CD = 0 and SES-CD = 1 was 2.0 (95% CI 0.35–11.36), 7.0 (95% CI 0.86–56.90) between SES-CD = 0 and SES-CD = 2, and 3.5 (95% CI 0.53–23.14) between SES-CD = 1 and SES-CD = 2. With regard to GHAS = 2, 9/9 (100%) patients with a SES-CD = 0 had GHAS ≤2, compared to 12/14 (85.7%) with a SES-CD = 1 and 3/9 (33.3%) with a SES-CD = 2; OR between SES-CD = 1 and SES-CD = 2 was 12.0 (95% CI 1.56–92.29). As for GHAS = 3, 14/14 (100%) patients with a SES-CD = 1 had GHAS ≤3 in contrast to 5/9 (55.6%)

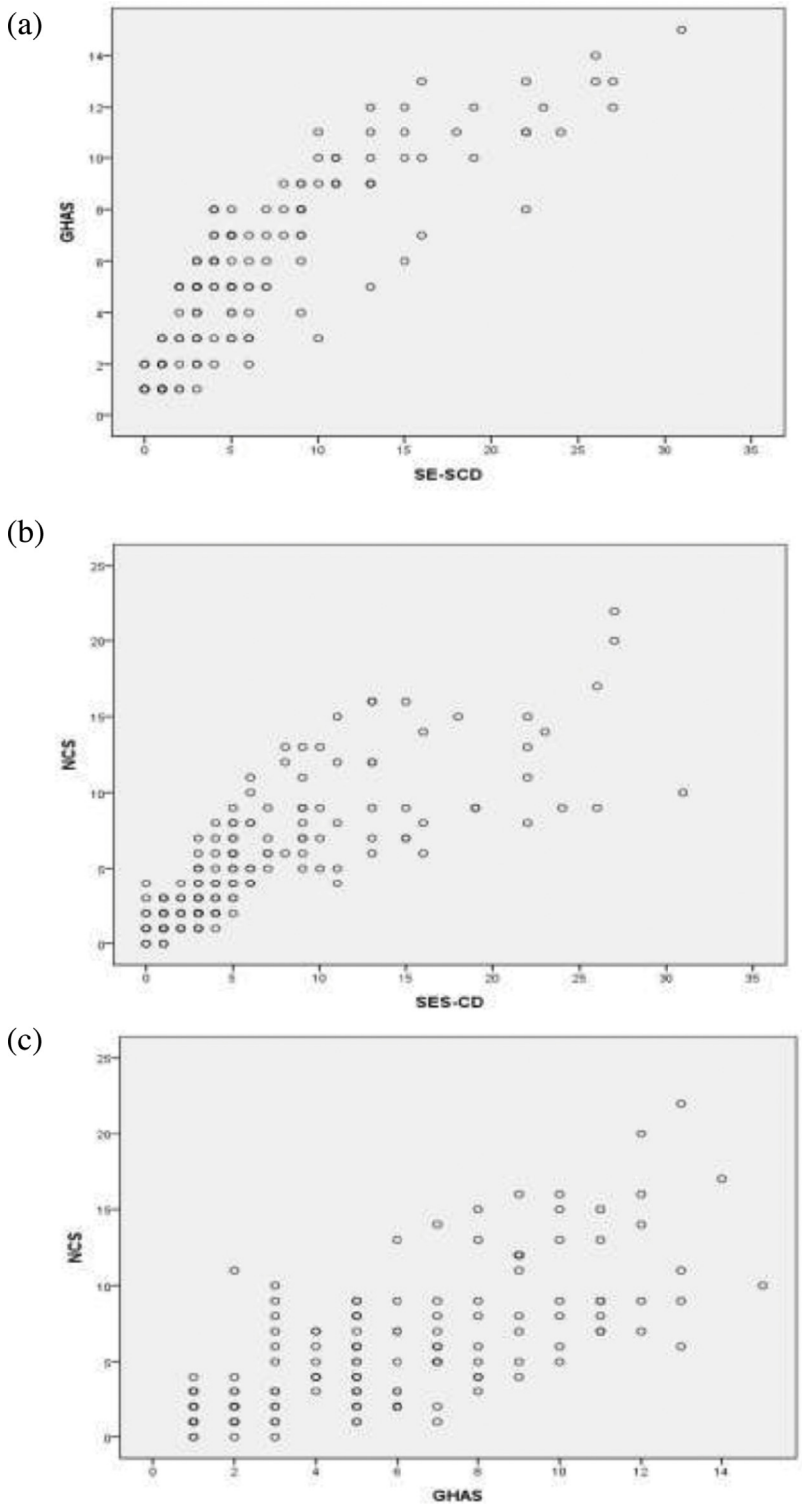

Fig. 3. Distribution, scatterplot and correlation coefficient (r) between SES-CD, GHAS and NCS.

with a SES-CD = 2. In addition, 6/9 (66.7%) patients with a SES-CD = 2 had GHAS ≤4. Collectively, these results indicated that SES-CD = 0 and SES-CD = 1 more approved a histological remission.

4. Discussion

Endoscopy and histopathology are vital for evaluating disease activity of Crohn's disease; however, few studies have investigated the correlation between endoscopic and histopathological indices of CD. In the present study, we found that there was a very strong correlation between endoscopy and histopathology and there was a strong correlation between the two histopathological indices that had been validated for disease activity of CD. In addition, the optimal SES-CD score that best correlated with histological remission was 0–1, which had potential prognostic significance.

The overall correlation between the SES-CD and GHAS was slightly stronger ($r = 0.86$; 95% CI 0.80–0.91, $p < 0.001$) than between the SES-CD and NCS ($r = 0.85$; 95% CI 0.81–0.88, $p < 0.001$), but the

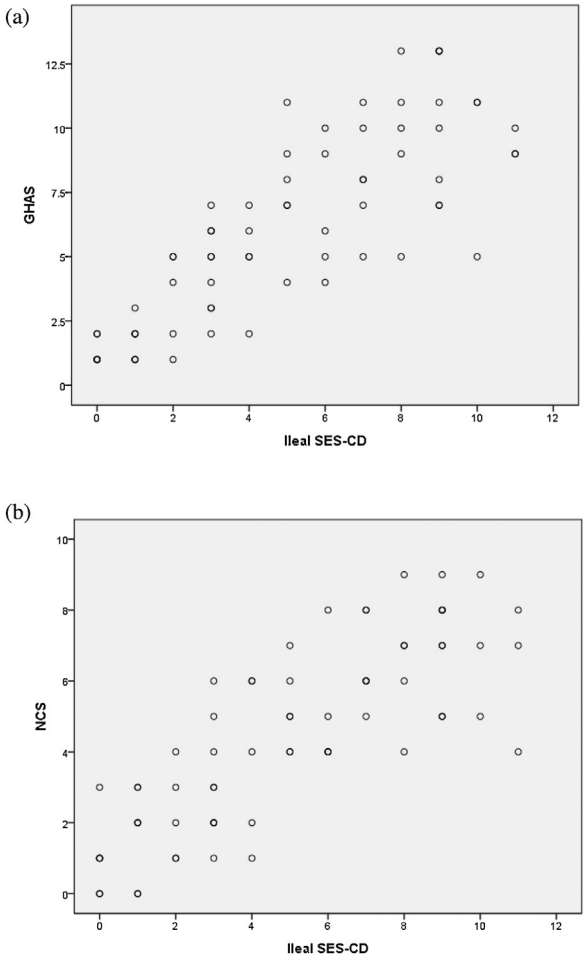

Fig. 4. Scatterplot and correlation coefficient (r) between ileal SES-CD, GHAS and NCS.

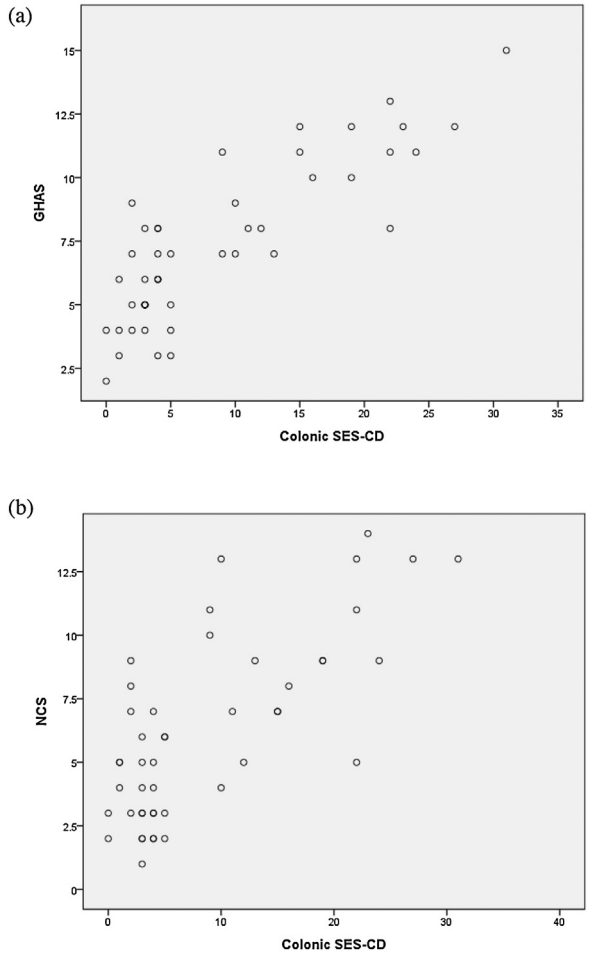

Fig. 5. Scatterplot and correlation coefficient (r) between colonic SES-CD, GHAS and NCS.

difference was not statistically significant. GHAS is the most commonly used histologic disease activity index in clinical research. A recent study investigated the association of histopathologic features with different CD4+ T cell subsets in colonic mucosal lamina propria for IBD patients [29]. This study included 26 CD patients with Crohn's colitis or ileocolitis, and demonstrated an excellent correlation between the ECAP (Extent, Chronicity, Activity and Plus) score and GHAS score ($r = 0.947$, $p < 0.001$). Although the GHAS were used in multiple studies, many modifications were performed and undergone verification test [30–34]. Moreover, we also analyzed the correlation between the GHAS or NCS and SES-CD for Crohn's ileitis and colitis respectively, and found that the correlation between GHAS and SES-CD was stronger than that between NCS and SES-CD in both Crohn's ileitis and colitis group. The reason for these results might be that there were similarities and differences as well between the GHAS and NCS. Both the GHAS and NCS describe architectural abnormalities, neutrophilic inflammation, and whether presence of erosion, ulcers or granulomas. However, the principal difference between the two is that NCS comprises many extra items, especially for eosinophils, which has been demonstrated to be highly correlated with the inflammatory response of UC [35], and others include Paneth cell or pyloric gland metaplasia, lymphoid nodules, muscularis mucosae hyperplasia and hyperplasia of endocrine cell hyperplasia. Although more widely, it will be more difficult to evaluate, thereby reducing the accuracy of the results.

Endoscopy plays a crucial role in the diagnosis and management of Crohn's disease, and it is the most widely used technique to evaluate the severity and the extent of CD. The CDEIS, first developed to assess the efficacy of corticosteroid therapy in a clinical trial [36], had been considered the gold standard for evaluating disease activity and mucosal healing of CD. However, the assessment of CDEIS is rather complicated, especially for the depth of ulcer, so the special training is required, which greatly limits the clinical application of CDEIS. As a result, the new SES-CD appeared to simplify the CDEIS. The calculation of SES-CD are easier and faster than that of CDEIS and the intraclass correlation between observers of the same colonoscopy procedure is better for the SES-CD. Moreover, SES-CD correlates better with histopathology and CDAI results than CDEIS [15,37]. The possible explanation may be that the SES-CD assesses the size of ulcer instead of its depth, and it is scored by selecting a number from 0 to 3, rather than by calculating the visual analogue scale, which is the most time-consuming step. Therefore, considering the above advantages, SES-CD was used as an index of endoscopic findings in the present study. In addition, this study also determined whether SES-CD $\leq$2 best represents remission, even though others considered that it could be 0–2 [26,27,38], which was important in clinical practice and research. A SES-CD of 0 or 1 was most closely related to histological remission. In this respect, 9/9 (100%) patients with a SES-CD = 0 had GHAS $\leq$4 and 14/14 (100%) patients with a SES-CD = 1, in contrast to 6/9 (66.7%) patients with a SES-CD = 2.

Admittedly, there were several limitations in this study. Firstly, the number of patients included was not large, especially in severe cases (17/143, SES-CD $\geq$16), and they were all Asian without other ethnic patient, which limited the external validity of the results.

Secondly, there was only a single endoscopist to evaluate the endoscopic score, which reduced variation of SES-CD, but there may be potential bias. Moreover, this was a single-institution retrospective study and thus larger prospective multi-centre studies were required.

In conclusion, notwithstanding the limitations outlined, this study demonstrates very strong correlation between endoscopic and histological indices, and the histopathologist can be confident that histological indices of the GHAS and NCS are as reliable as each other. In addition, a SES-CD score 0 or 1 best defines the mucosal healing without histological disease activity that indicates a good clinical outcome in the following years.

Conflict of interest

None declared.

Funding sources

The work was supported by grants from the Key Project of Jiangsu Social Development (BE2016752) and Innovation Project of Military Medicine (16CXZ007).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.01.010.

References

[1] Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR guideline for diagnostic assessment in inflammatory bowel disease. J Crohns Colitis 2018;(August), http://dx.doi.org/10.1093/ecco-jcc/jjy113 [Epub ahead of print].
[2] Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;380(9853):1590–605.
[3] Neurath MF, Travis SPL. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012;61(11):1619–35.
[4] Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with earlystage Crohn's disease. Gastroenterology 2010;138(2):463–8, quiz e10-1.
[5] Peyrin-Biroulet L, Ferrante M, Magro F, Campbell S, Franchimont D, Fidder H, et al. Results from the 2nd Scientific Workshop of the ECCO (I): impact of mucosal healing on the course of inflammatory bowel disease. J Crohns Colitis 2011;5(5):477–83.
[6] Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99(4):956–63.
[7] Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142(5), 1102-1111.e2.
[8] Hébuterne X, Lémann M, Bouhnik Y, Dewit O, Dupas JL, Mross M, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohnés disease following treatment with certolizumab pegol. Gut 2013;62(2):201–8.
[9] Ferrante M, Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. Gastroenterology 2013;145(5):978–86.
[10] Gomes P, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut 1986;27(1):92–5.
[11] Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohnös disease. Gastroenterology 2002;122(2):512–30.
[12] Korelitz BI, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. J Clin Gastroenterol 1984;6(2):123–7.
[13] Molander P, Sipponen T, Kemppainen H, Jussila A, Blomster T, Koskela R, et al. Achievement of deep remission during scheduled maintenance therapy with TNF TNFα-blocking agents in IBD. J Crohns Colitis 2013;7(9):730–5.
[14] Durko L, Stasikowska-Kanicka OA, Wagrowska-Danilewicz M, Danilewicz M, Małecka-Panas El. An analysis of the correlation of clinical, endoscopic and histological classifications in Crohn's disease. Prz Gastroenterol 2013;8(6):377–82.
[15] Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60(4):505–12.
[16] Khanna R, Zou G, Stitt L, Feagan BG, Sandborn WJ, Rutgeerts P, et al. Responsiveness of endoscopic indices of disease activity for Crohn's disease. Am J Gastroenterol 2017;112(10):1584–92.
[17] Dubcenco E, Zou G, Stitt L, Baker JP, Jeejeebhoy KN, Kandel G, et al. Effect of standardised scoring conventions on inter-rater reliability in the endoscopic evaluation of Crohn's disease. J Crohns Colitis 2016;10(9):1006–14.
[18] Daperno M, Comberlato M, Bossa F, Biancone L, Bonanomi AG, Cassinotti A, et al. Inter-observer agreement in endoscopic scoring systems: preliminary report of an ongoing study from the Italian Group for Inflammatory Bowel Disease (IG-IBD). Dig Liver Dis 2014;46(11):969–73.
[19] Khanna R, Zou G, D'Haens G, Rutgeerts P, McDonald JW, Daperno M, et al. Reliability among central readers in the evaluation of endoscopic findings from patients with Crohn's disease. Gut 2016;65(7):1119–25.
[20] Rutgeerts P, Reinisch W, Colombel JF, Sandborn WJ, D'Haens G, Petersson J, et al. Agreement of site and central readings of ileocolonoscopic scores in Crohn's disease: comparison using data from the EXTEND tria. Gastrointestinal Endoscopy 2016;83(1):188–97.
[21] Sipponen T, Nuutinen H, Turunen U, Färkkilä M. Endoscopic evaluation of Crohnäs disease activity: comparison of the CDEIS and the SES-CD. Inflamm Bowel Dis 2010;16(12):2131–6.
[22] Lee JS, Kim ES, Moon W. Chronological review of endoscopic indices in inflammatory bowel disease. Clin Endosc 2018;(August), http://dx.doi.org/10.5946/ce.2018.042 [Epub ahead of print].
[23] D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology 1998;114(2):262–7.
[24] Naini BV, Cortina G. A histopathologic scoring system as a tool for standardized reporting of chronic (ileo) colitis and independent risk assessment for inflammatory bowel disease. Hum Pathol 2012;43(12):2187–96.
[25] Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's Disease 2016: part 1: diagnosis and medical management. J Crohns Colitis 2017;11(1):3–25.
[26] Moskovitz DN, Daperno M, Van Assche G. Defining and validating cut-offs for the simple endocopic score for Crohn's disease. Gastroenterology 2007;132:S1097.
[27] Vuitton L, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. Gut 2016;65(9):1447–55.
[28] Brown RA, Swanson-Beck J. Medical statistics on personal computers. 2nd edn. London: BMJ Publishing Group; 1993.
[29] Gui X, Li J, Ueno A, Iacucci M, Qian J, Ghosh S. Histopathologic features of inflammatory bowel disease are associated with different CD4+ T cell subsets in colonic mucosal lamina propria. J Crohns Colitis 2018;12(12):1448–58.
[30] Geboes K, Rutgeerts P, Opdenakker G, Olson A, Patel K, Wagner CL, et al. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. Curr Med Res Opin 2005;21(11):1741–54.
[31] Sipponen T, Karkkainen P, Savilahti E, Kolho KL, Nuutinen H, Turunen U, et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharm Therap 2008;28(10):1221–9.
[32] Mantzaris GJ, Christidou A, Sfakianakis M, Roussos A, Koilakou S, Petraki K, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. Inflamm Bowel Dis 2009;15(3):375–82.
[33] Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136(2):441–50.
[34] Laharie D, Reffet A, Belleannee G, Chabrun E, Subtil C, Razaire S, et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Aliment Pharm Therap 2011;33(6):714–21.
[35] Roberts-Thomson IC, Fon J, Uylaki W, Cummins AG, Barry S. Cells, cytokines and inflammatory bowel disease: a clinical perspective. Expert Rev Gastroenterol Hepatol 2011;5(6):703–16.
[36] Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989;30:983–9.
[37] Sipponen T, Nuutinen H, Turunen U, Färkkilä M. Endoscopic evaluation of Crohn's disease activity: comparison of the CDEIS and the SES-CD. Inflamm Bowel Dis 2010;16(12):2131–6.
[38] Af Björkesten C-G, Nieminen U, Turunen U, Arkkila P, Sipponen T, Färkkilä M. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. Scand J Gastroenterol 2012;47:528–37.