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Original

Can inflammatory markers and clinical indices serve as useful referral criteria for leukocyte scan in patients with inflammatory bowel disease?

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Abstract

BACKGROUND: In the follow-up of patients with inflammatory bowel disease (IBD), Tc-99m-HMPAO labelled leukocytes scintigraphy (leukocyte scan; LS) has long been established as a valuable diagnostic tool. The aim of this study was to estimate the relationship between scintigraphic results, inflammatory markers (IM) (including white blood cells (WBCs) and C-reactive protein (CRP)), clinical parameters and clinical indices of the disease activity (CI), in order to determine clinical settings in which LS is indicated.

MATERIAL AND METHODS: A total of 147 patients who underwent LS, (79 males, 68 females, median age 36), were examined from April 2010 until December 2017 at the University Hospital Centre Zagreb, Croatia. Among these, 126 (86%) had Crohn's disease (CD), and 21 (14%) had ulcerative colitis (UC). Either increased IM (either WBCs $\geq 10x10^9$/L and/or CRP ≥ 7.4 mg/L) and/or CI, Crohn's disease activity index (CDAI) score ≥ 220 points, Harvey-Bradshaw index (HBI) score ≥ 8 points, and severe colitis defined according to Truelove and Witts' criteria (TWC) for UC, respectively, were considered consistent with active disease.

RESULTS: Eighty-two patients (56%) had negative scans, while in 65 (44%) the scans were positive. Positive correlations were found between LS and all of the three parameters, WBCs, CRP and CI. When combined, the three parameters demonstrated even stronger positive correlation with the LS results with the correlation coefficient 0.76 ($p < 0.0001$, 95% CI 0.68–0.82). Using endoscopy and histological study findings of the obtained specimens as a composite reference standard, the overall sensitivity, specificity, positive predictive value and negative predictive value of IM and CI for LS were determined, being 91%, 85%, 83%, and 92%, respectively. IM and CI were both negative in 76 (52%) out of the total subjects. Of these, 70 had negative LS as well.

CONCLUSIONS: In the presence of normal IM (WBCs $< 10 \times 10^9$/L and CRP < 7.4 mg/L) with CI indicating no active or mildly active disease, LS is not necessarily indicated. Clinical parameters individually are not sufficient in defining accurate criteria for performing LS.

KEY words: inflammatory bowel disease; Crohn's disease; Ulcerative colitis; leukocyte scan; white blood cells scintigraphy; inflammatory markers

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Introduction

Inflammatory bowel disease (IBD) includes three clinical entities: Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis [1]. With its increasing incidence, IBD represents a great challenge with regards to the selection of appropriate first-line and follow-up diagnostic methods [2]. The diagnostic methods that are mostly invasive [3, 4] have an impact on patients quality of life, which is already impaired [5, 6] by nature and hardly predictable course of the disease [7]. The advantages of nuclear medicine imaging with Tc-99m-HMPAO labelled leukocytes (leukocyte scan; LS) in the follow-up of patients with IBD are noninvasiveness, no need for patient preparation, relatively low radiation exposure compared to radiological methods and the possibility of visualization of the

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disease activity in all segments of the gastrointestinal system. Moreover, the imaging is not contraindicated in active or acute phases of IBD and represents no risk of potential complications (i.e. bowel perforation and haemorrhage) [8]. Furthermore, this method can differentiate active inflammation from fibrotic bowel strictures [9].

Inflammatory markers and various indices of the disease activity are commonly used in the clinical work-up of these patients [10]. It is not clear how they affect clinicians' decision of whether to use or not LS in patients with IBD.

The aim of this study was to estimate the relationship between scintigraphic results, inflammatory markers (IM) [including white blood cells (WBCs) and C-reactive protein (CRP)], clinical parameters and clinical indices of the disease activity (CI), in order to determine clinical settings in which LS is indicated.

Material and methods

Patients. This retrospective study was conducted at the University Hospital Centre Zagreb, Croatia. All subjects provided written informed consent. Only patients with endoscopic findings and histological studies of the obtained biopsy specimens with proven IBD and laboratory assessment were included in this study. Patients who were only suspected of having IBD, but had not undergone endoscopy, or patients who underwent endoscopy that did not prove IBD, were excluded. A total of 147 patients, (79 males, 68 females, median age 36), were examined from April 2010 until December 2017. Among these, 126 (86%) had CD, and 21 (14%) had UC. WBCs and CRP values were determined 1 to 3 days before LS. WBCs $\geq 10 \times 10^9$/L and CRP (using specified limits) ≥ 7.4 mg/L were considered consistent with active disease. Clinical parameters evaluated in the study were age, gender, duration of the disease, abdominal pain, number of stools per day, stool quality, extraintestinal findings or complications, bowel resection and body temperature. CI scores were classified as positive with Crohn's disease activity index (CDAI) score ≥ 220 points, Harvey-Bradshaw index (HBI) score ≥ 8 points, and severe colitis defined according to Truelove and Witts' criteria (TWC) for UC [11]. The clinical characteristics of the patients included in this study are shown in Table 1.

Tc-99m-HMPAO labelled leukocytes scanning. The standard protocol was used for scanning of all patients. Images were acquired using dual-headed SPECT/CT γ camera Symbia (Siemens, T2) and dual-headed SPECT γ camera E cam (Siemens), both fitted with low energy, high-resolution collimators. Scintigraphy was performed with Tc-99m-HMPAO labelled leukocytes. Fifty millilitres of venous blood was taken from the patient, separated, and WBCs labelled with 750–1000 MBq Tc-99m-HMPAO (Ceretec, GE Healthcare, Little Chalfont, UK), followed by the labelled cells being reinjected intravenously in recommended dose (about 370 MBq) [12]. Planar abdominal images were acquired at 1/2, 1, 2, 3, 4, and 24 h postinjection. The scan results were considered positive in the presence of consistently increased radiopharmaceutical uptake in any part of the intestines that was seen on at least three consecutive scans of the study. Otherwise, the scintigraphic findings were considered negative. The results were assessed qualitatively by experienced nuclear medicine specialists and were analysed comparatively with the selected clinical and laboratory parameters.

Statistical analysis. Statistical analysis was carried out using MedCalc (version 12.1.3 MedCalc Software, MariaKerke, Belgium). Depending on the type of variables, their intersection was analysed using Pearson's and Spearman's correlation coefficient. Logistic regression was applied to determine which variables may predict the scintigraphic results. Receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated with threshold CRP value depending on scintigraphic findings. P-value was considered statistically significant if < 0.05.

Results

Out of a total of 147 patients, 82 (56%) had negative scans, while in 65 (44%) the scans were positive. The clinicopathological features of the patients are shown in Table 2. Scans indicating active CD and UC are shown in Figure 1 and Figure 2.

LS findings were compared with the values of IM, using the upper limits for normality for WBCs as $10x10^9$/L and specified limits for CRP as 7.4 mg/L, based on ROC curve analysis (AUC 0.784, 95% CI 0.71–0.85, $p < 0.0001$) in order to set threshold with the highest sensitivity and specificity.

Positive correlations were found between LS and all of the three parameters, WBCs, CRP and CI. When combined, the three parameters demonstrated even stronger positive correlation with the LS results, with the correlation coefficient 0.76 ($p < 0.0001$, 95% CI 0.68–0.82). Using endoscopy and histological study findings of the obtained specimens as a composite reference standard, the overall sensitivity, specificity, positive predictive value and negative predictive value of IM and CI for LS were determined, being 91%, 85%, 83%, and 92%, respectively. IM and CI were both negative in 76 (52%) out of a total of 147 subjects. Of these, 70 had negative LS as well.

Table 3 shows the comparison of LS results with both IM and CI scores. These results show that of the 82 patients with negative LS, 70 (85%) had normal both IM and CI. However, there were six patients with normal IM and CI who had positive LS. Of the 65 patients with positive LS, 59 (91%) had elevated either IM and/or CI. Twelve patients had elevated IM and/or CI and negative findings on LS.

Multivariable analysis of clinicopathological parameters showed that IM and CI were both predictive for the positive LS. Patient's age, gender, duration of the disease, abdominal pain, number of stools per day, stool quality, extraintestinal findings or complications, bowel resection, and body temperature had no predictive capacity for LS.

Discussion

Within the wide range of different diagnostic tests that are commonly used in diagnosing IBD, endoscopy is considered to play the central role [13]. Once the definitive diagnosis is proven, a continuous follow-up throughout the entire patient's life is necessary, as the disease is known for its unpredictable nature, with a variety of possible complications that may occur along its course [1]. Various biomarkers have been proposed for the disease activity assessment in IBD patients [14, 15]. As well, there are studies that investigate the issues of rational balancing of benefits and risks with

Table 1. The clinical characteristics of the patients

	No. of patients
Sex	
Male	79 (54%)
Female	68 (46%)
Age	
≤ 40	94 (64%)
> 40	53 (36%)
Duration of illness	
< 5 years	68 (46%)
> 5 years	79 (54%)
Pain	
No	79 (54%)
Yes	68 (46%)
No. of stools per day	
≤ 3	112 (76%)
> 3	35 (24%)
Quality of stools	
Normal	57 (39%)
Pathological	90 (61%)
Surgical interventions[b]	
No	97 (66%)
Yes	50 (34%)
Complications[b]	
No	97 (66%)
Yes	50 (34%)
Inflammatory markers[d]	
WBC < 10×10^9/L and CRP < 7.4 mg/L	83 (56%)
either WBC ≥ 10×10^9/L and/or CRP ≥ 7.4 mg/L	64 (44%)
Clinical index score[e]	
Normal/Mild[f]	106 (72%)
Moderate/Severe[g]	41 (28%)

WBCs — white blood cells; CRP — C-reactive protein; [a] — liquid/soft/mucous stool, normal stool with an admixture of blood and/or mucus; [b] — bowel resections, ileostomy, resections of fistulous channels etc.; [c] — arthritis, arthralgias, iritis, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure, fistula, or abscess, another fistula; [d] — WBCs and CRP; [e] — Crohn's disease activity index (CDAI), Harvey-Bradshaw index (HBI) for Crohn's disease; Truelove and Witts' criteria (TWC) for ulcerative colitis; [f] — Mildly active disease (only in patients with CD); CDAI score between 150–220; HBI score between 5–7; [g] — Moderate/Severe; CDAI scores ≥ 220 points, HBI score ≥ 8 points and severe colitis defined according to TWC

regards to the quality of life, cost-effectiveness, availability and accessibility of diagnostic tests, and radiation exposure considerations [16]. As a result, besides endoscopic assessment of the disease, in both the initial diagnosis and the follow-up of IBD patients, different combinations of laboratory testing, faecal biomarkers and imaging tools have been proposed, in addition to clinical features [10]. Although known to be non-specific, WBCs and CRP are considered easily available, simple, inexpensive and sufficiently reliable markers in predicting the disease activity [17]. Nowadays, in addition to WBCs and CRP, faecal calprotectin and lactoferrin, relatively new inflammatory markers, are widely accepted for common use. However, at the time of inclusion of our patients in the study, the two markers were not routinely used at our facility. Our aim was to estimate the relationship between scintigraphic results, IM, clinical parameters and CI, in order to determine in which clinical settings LS is indicated.

In 70 (48%) of 147 patients who had CDAI scores < 220 points, HBI scores < 8 points, and mild to moderate colitis defined according to TWC, associated with normal levels of IM, LS was negative. However, 6 (4%) out of 147 patients who had IM within the normal range, whereas CI were not increased, had positive LS.

The results of several previous studies indicate that in the follow-up process of the selected IBD patients, as an alternative to invasive procedures, a set of different imaging methods, including LS, may yield sufficient diagnostic information regarding the extent and the activity of the disease, as well as regarding treatment

Table 2. The clinicopathological features of the IBD patients according to LS results

	Negative scintigraphy		Positive scintigraphy		*P* value
	CD	UC	CD	UC	
Patients	69	13	57	8	< 0.0001
Duration of illness					
< 5 years	34	7	24	3	0.754
> 5 years	35	6	33	5	
Pain					
No	47	7	24	1	0.002
Yes	22	6	33	7	
No. of stools per day					
≤ 3	56	10	42	4	0.244
> 3	13	3	15	4	
Quality of stools					
Normal	34	4	18	1	0.068
Pathological	35	9	39	7	
Surgical interventions					
No	41	12	36	8	0.021
Yes	28	1	21	0	
Complications					
No	44	10	37	6	0.761
Yes	25	3	20	2	
Inflammatory markers					
WBC < 10×10^9/L and CRP < 7.4 mg/L	61	9	11	2	< 0.0001
either WBC ≥ 10×10^9/L and/or CRP ≥ 7.4 mg/L	8	4	46	6	
Clinical index score					
Normal/Mild	66	12	26	2	< 0.0001
Moderate/Severe	3	1	31	6	

CD — Crohn's disease; UC — ulcerative colitis; WBCs — white blood cells; CRP — C-reactive protein;

response [8]. In an individual algorithm for IBD patients' follow-up, LS can be positioned at a high level, due to its comparability both to radiological methods and to endoscopy [18]. With its high accuracy of 92–100%, a sensitivity of 95–100% and a specificity of 85–100% [8], LS can be used as an alternative to the conventional and cross-sectional radiological methods for the disease evaluation [19]. Furthermore, according to the results that Rispo et al. had published, a multimodality imaging approach based on using complementary noninvasive methods exhibits increased sensitivity and specificity. For the diagnosis of the CD, the authors reported a combined, 100% sensitivity and specificity of LS and ultrasound, when the two are used together, as complementary imaging tools [20]. Therefore, in the follow-up of patients with IBD, obtaining accurate information regarding the disease activity should be considered by using either one or more complementary non-invasive imaging techniques as an alternative to endoscopy, which may be of interest in rationalizing the use of invasive procedures, taking also into consideration the quality-of-life-aspects that are impaired in multiple ways [6]. Among these, LS has long been established as a valuable diagnostic tool. Our results suggest that in selected IBD patients, the inflammation activity of the disease may be assessed by measuring IM, followed by LS imaging, after that leading to no additional and further diagnostic testing, as one of the possible outcomes. Our results also indicate that IM and CI may be used as an easy, quick and inexpensive screening orientation tool with the purpose to determine whether LS itself would be necessary and indicated. Such results, if confirmed by further clinical research, may be incorporated in developing algorithms for the rational diagnosis, follow-up, and monitoring of IBD patients.

In conclusion, in the presence of normal IM (WBCs < 10×10^9/L and CRP < 7.4 mg/L) with CI indicating no active or mildly active disease, LS is not necessarily indicated. Clinical parameters individually are not sufficient in defining accurate criteria for performing LS.

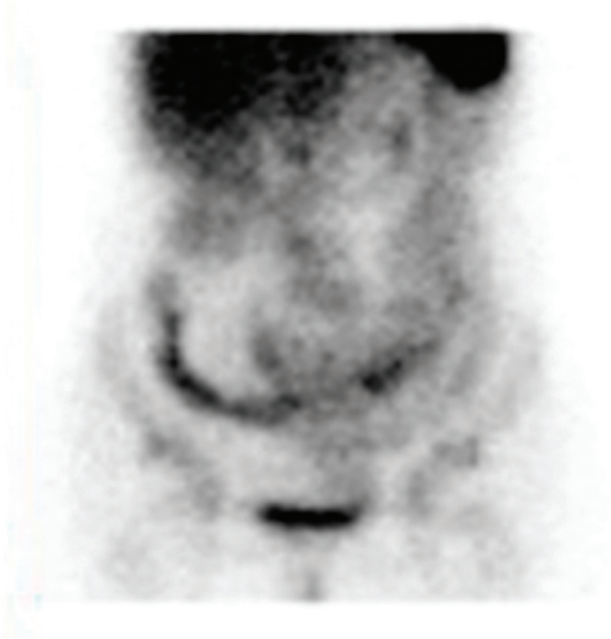

Figure 1. LS in 46-year-old female patient diagnosed with Crohn's disease. Increased uptake of labelled WBCs is seen in the terminal ileum and ascending colon

Figure 2. LS in 27-year-old male patients, diagnosed with ulcerative colitis. Increased uptake of labelled WBCs is seen in the descending and the sigmoid colon

Table 3. A comparison of LS results with both IM and CI scores

	Negative scintigraphy (n = 82)	Positive scintigraphy (n = 65)	Total (n = 147)	*P* value
WBC < 10 × 10^9/L, CRP < 7.4 mg/L and CDAI < 220, HBI < 7 and mild to moderate colitis according to TWC	70 (85%)	6 (9%)	76 (52%)	< 0.0001
Either WBC ≥ 10 × 10^9/L, and/or CRP ≥ 7.4 mg/L, and/or CDAI ≥ 220, HBI ≥ 8 and severe colitis according to TWC	12 (15%)	59 (91%)	71 (48%)	< 0.0001

WBCs — white blood cells; CRP — C-reactive protein; CDAI — Crohn's disease activity index; HBI — Harvey-Bradshaw index; TWC — Truelove and Witt's criteria

References

1. Viscido A, Aratari A, Maccioni F, et al. Inflammatory bowel diseases: clinical update of practical guidelines. Nucl Med Commun. 2005; 26(7): 649–655, doi: 10.1097/01.mnm.0000169205.21377.6a, indexed in Pubmed: 15942486.
2. Karlinger K, Györke T, Makö E, et al. The epidemiology and the pathogenesis of inflammatory bowel disease. European Journal of Radiology. 2000; 35(3): 154–167, doi: 10.1016/s0720-048x(00)00238-2.
3. Hommes DW, van Deventer SJH. Endoscopy in inflammatory bowel diseases. Gastroenterology. 2004; 126(6): 1561–1573, doi: 10.1053/j.gastro.2004.03.023, indexed in Pubmed: 15168367.
4. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. Gastroenterology. 2007; 133(5): 1670–1689, doi: 10.1053/j.gastro.2007.09.001, indexed in Pubmed: 17983810.
5. Bernklev T, Jahnsen J, Lygren I, et al. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. Inflamm Bowel Dis. 2005; 11(10): 909–918, doi: 10.1097/01.mib.0000179467.01748.99, indexed in Pubmed: 16189421.
6. Becker HM, Grigat D, Ghosh S, et al. Living with inflammatory bowel disease: A Crohn's and Colitis Canada survey. Can J Gastroenterol Hepatol. 2015; 29(2): 77–84, doi: 10.1155/2015/815820, indexed in Pubmed: 25803017.
7. Golovics PA, Mandel MD, Lovasz BD, et al. Inflammatory bowel disease course in Crohn's disease: is the natural history changing? World J Gastroenterol. 2014; 20(12): 3198–3207, doi: 10.3748/wjg.v20.i12.3198, indexed in Pubmed: 24696605.
8. Stathaki MI, Koukouraki SI, Karkavitsas NS, et al. Role of scintigraphy in inflammatory bowel disease. World J Gastroenterol. 2009; 15(22): 2693–2700, doi: 10.3748/wjg.15.2693, indexed in Pubmed: 19522018.
9. Annovazzi A, Bagni B, Burroni L, et al. Nuclear medicine imaging of inflammatory/infective disorders of the abdomen. Nucl Med Commun. 2005; 26(7): 657–664, doi: 10.1097/01.mnm.0000169202.68011.47, indexed in Pubmed: 15942487.
10. Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clin Gastroenterol Hepatol. 2016; 14(3): 348–354.e17, doi: 10.1016/j.cgh.2015.06.001, indexed in Pubmed: 26071941.

11. Magro F, Gionchetti P, Eliakim R, et al. European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis. 2017; 11(6): 649–670, doi: 10.1093/ecco-jcc/jjx008, indexed in Pubmed: 28158501.
12. de Vries EFJ, Roca M, Jamar F, et al. Guidelines for the labelling of leucocytes with (99m)Tc-HMPAO. Inflammation/Infection Taskgroup of the European Association of Nuclear Medicine. Eur J Nucl Med Mol Imaging. 2010; 37(4): 842–848, doi: 10.1007/s00259-010-1394-4, indexed in Pubmed: 20198473.
13. Moran CP, Neary B, Doherty GA. Endoscopic evaluation in diagnosis and management of inflammatory bowel disease. World J Gastrointest Endosc. 2016; 8(20): 723–732, doi: 10.4253/wjge.v8.i20.723, indexed in Pubmed: 28042386.
14. Viennois E, Zhao Y, Merlin D. Biomarkers of Inflammatory Bowel Disease: From Classical Laboratory Tools to Personalized Medicine. Inflamm Bowel Dis. 2015; 21(10): 2467–2474, doi: 10.1097/MIB.0000000000000444, indexed in Pubmed: 25985250.
15. Fengming Yi, Jianbing Wu. Biomarkers of inflammatory bowel disease. Dis Markers. 2014; 2014: 710915, doi: 10.1155/2014/710915, indexed in Pubmed: 24963213.
16. Haas K, Rubesova E, Bass D. Role of imaging in the evaluation of inflammatory bowel disease: How much is too much? World J Radiol. 2016; 8(2): 124–131, doi: 10.4329/wjr.v8.i2.124, indexed in Pubmed: 26981221.
17. Cappello M, Morreale GC. The Role of Laboratory Tests in Crohn's Disease. Clin Med Insights Gastroenterol. 2016; 9: 51–62, doi: 10.4137/CGast.S38203, indexed in Pubmed: 27656094.
18. Becker W, Fischbach W, Weppler M, et al. Radiolabelled granulocytes in inflammatory bowel disease: diagnostic possibilities and clinical indications. Nucl Med Commun. 1988; 9(10): 693–701, doi: 10.1097/00006231-198810000-00004, indexed in Pubmed: 3062507.
19. Panes J, Bouhnik Y, Reinisch W, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. J Crohns Colitis. 2013; 7(7): 556–585, doi: 10.1016/j.crohns.2013.02.020, indexed in Pubmed: 23583097.
20. Rispo A, Imbriaco M, Celentano L, et al. Noninvasive diagnosis of small bowel Crohn's disease: combined use of bowel sonography and Tc-99m-HMPAO leukocyte scintigraphy. Inflamm Bowel Dis. 2005; 11(4): 376–382, doi: 10.1097/01.mib.0000164020.65106.84, indexed in Pubmed: 15803028.