Association of MMP9, HsCRP, and ESR with 5-ASA Treatment Duration and Disease Activity Based on Truelove and Witts Criteria in Patients With Diagnosed Ulcerative Colitis

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ABSTRACT

Background: *The American College of Gastroenterology (ACG) currently recommends the Truelove and Witts scoring system for evaluating Ulcerative Colitis (UC) disease activity. Inflammatory markers such as Matrix Metallopeptidase 9 (MMP-9), High-sensitivity C-Reactive Protein (HsCRP), and Erythrocyte Sedimentation Rate (ESR) have previously been shown to correlate with intestinal inflammation. To evaluate the association of MMP-9, HsCRP, and LED with disease activity and treatment duration in UC according to the Truelove and Witts criteria.*

Methods: *An observational analytic study with a cross-sectional design was conducted involving subjects with UC diagnosed pathologically and receiving 5-ASA therapy at the Gastroenterohepatology Outpatient Department of Dr. Soetomo Hospital. MMP-9, HsCRP, and ESR serum levels were measured. The disease activity was determined based on the Truelove and Witts criteria. Analysis was done by spearman's correlation. P-values and correlation coefficients (r) were presented.*

Results: *Among the 31 subjects, the majority were female (67.7%) with an average age of 46.84 years. Approximately 35.5% subjects had been treated for more than 6 months. The MMP-9 and HsCRP serum levels were above normal range (71% and 93.5% subjects, respectively). The majority (74.2%) of the subjects had normal ESR levels. Among the investigated inflammatory markers, only ESR levels significantly had a very weak positive correlation (p=0.010; r=0.004).*

Conclusion: *ESR serves as an effective biomarker for UC disease activity compared to MMP-9 and HsCRP. Further study is warranted to explore the role of these biomarkers in UC management.*

Keywords: *ESR, HsCRP, MMP-9, Truelove and Witts, ulcerative colitis*

ABSTRAK

Latar Belakang: *American College of Gastroenterology (ACG) saat ini merekomendasikan sistem penilaian Truelove dan Witts untuk mengevaluasi aktivitas penyakit kolitis ulseratif. Penanda inflamasi seperti Matrix Metallopeptidase 9 (MMP-9), High-sensitivity C-Reactive Protein (HsCRP), dan Erythrocyte Sedimentation Rate (ESR) sebelumnya telah terbukti berkorelasi dengan inflamasi usus. Untuk mengevaluasi hubungan MMP-*

9, HsCRP, dan LED dengan aktivitas penyakit dan durasi pengobatan pada kolitis ulseratif menurut kriteria Truelove dan Witts.

Metode: *Penelitian analitik observasional dengan desain cross-sectional dilakukan dengan melibatkan subjek dengan kolitis ulseratif yang didiagnosis secara patologis dan menerima terapi 5-ASA di Departemen Gastroenterohepatologi Rawat Jalan RSUD Dr. Soetomo. Kadar MMP-9, HsCRP, dan ESR serum diukur. Aktivitas penyakit ditentukan berdasarkan kriteria Truelove dan Witts. Analisis dilakukan dengan korelasi spearman. Nilai-p dan koefisien korelasi (r) disajikan.*

Hasil: *Di antara 31 subjek, mayoritas adalah perempuan (67,7%) dengan usia rata-rata 46,84 tahun. Sekitar 35,5% subjek telah dirawat selama lebih dari 6 bulan. Kadar serum MMP-9 dan HsCRP berada di atas kisaran normal (masing-masing 71% dan 93,5% subjek). Mayoritas (74,2%) subjek memiliki kadar LED normal. Di antara penanda inflamasi yang diteliti, hanya kadar LED yang secara signifikan memiliki korelasi positif yang sangat lemah (p=0,010; r=0,004).*

Simpulan: *LED berfungsi sebagai biomarker yang efektif untuk aktivitas penyakit kolitis ulseratif dibandingkan dengan MMP-9 dan HsCRP. Penelitian lebih lanjut diperlukan untuk mengeksplorasi peran biomarker ini dalam manajemen kolitis ulseratif.*

Kata kunci: *ESR, HsCRP, MMP-9, Truelove and Witts, kolitis ulseratif*

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a chronic inflammatory gastrointestinal tract disease associated with an abnormal immune response to the intestinal microflora. IBD is divided into Ulcerative Colitis (UC) and Crohn's Disease (CD).[1] Epidemiologically, UC cases are more numerous than those with CD, with the prevalence of UC in Indonesia reaching 8.2% of all patients undergoing colonoscopy.[2] Current management of UC aims to achieve symptomatic remission and control asymptomatic inflammation.[3] UC therapy focuses on controlling the degree of inflammation to prolong remission and prevent hospitalization and surgery. The American College of Gastroenterology (ACG) guidelines recommends the use of endoscopy and a scoring system to assess UC disease activity.[4] Many scoring systems for UC involve invasive endoscopy and require complex patient preparation, namely UCEIS and Mayo index.[5] Truelove and Witts is a non-invasive assessment of clinical activity based on individual complaints, objective signs, and laboratory results. Recent reports have shown that endoscopic examinations add little information of UC disease activity. An accurate evaluation can be obtained with clinical markers alone. Clinical markers showed a significant decrease after therapy in UC patients compared to baseline values.[4]

Laboratory parameters can reduce the frequency of endoscopy, increase the objectivity of analysis, improve patient comfort, and reduce the cost of care. Some of the biological markers that have been widely studied and used to monitor UC disease activity are Matrix Metalloproteinase 9 (MMP-9), Erythrocyte Sedimentation Rate (ESR), and High-sensitivity C-Reactive Protein (HsCRP). MMP-9 has been widely documented as a major metalloproteinase associated with IBD development. Studies in mice deficient in MMP-9 showed that MMP-9 was involved in the early stages of IBD development. However, the exact mechanism is unclear.[6] MMP contributes greatly to mucosal degradation in UC.[7] Therefore, MMP-9 is used as a potential diagnostic and therapeutic target in UC. In addition, HsCRP and ESR examinations are other non-invasive and commonly available examinations that can be used to detect disease activity in UC.

Study to evaluate the association between HsCRP and ESR serum levels with the Truelove and Witts criteria were still limited. Until this study was conducted, there was still no study that clearly linked MMP-9, HsCRP, and ESR serum levels to the treatment duration and disease activity in UC. Therefore, our study was done to analyze the association between MMP-9, ESR, and HsCRP serum levels with the treatment duration and disease activity from the Truelove and Witts criteria.

METHODS

An observational analytic study with cross-sectional design conducted at the Gastroenterohepatology Outpatient Department at Dr. Soetomo Hospital from April to December 2023. The subjects were patients with UC diagnosed by anatomical pathology, aged ≥18

years, and undergoing treatment with 5-ASA, and were willing to participate and sign an informed consent. Contraindications to endoscopy, other drug usage for UC, smoking or alcohol consumption, metabolic syndrome, obesity, cancer, diabetes, rheumatic, cerebrovascular, autoimmune, cardiac, and psychiatric diseases were excluded. The consecutive sampling technique was used to obtain a minimum of 28 subjects. This study passed the ethical clearance from Ethic Committee of Health Research Dr. Soetomo Hospital Surabaya (0820/KEPK/XI/2023).

Subjects were given 5-ASA and assessed for disease activity based on Truelove and Witts criteria. Blood samples were taken for MMP-9, ESR, and HsCRP serum levels at the Gastroenterohepatology Outpatient Department at Dr. Soetomo Hospital, then sent to the Prodia Lab Surabaya. MMP-9 levels detection was performed using the ELISA method. The independent variables were MMP-9, HsCRP, and ESR serum levels, while the dependent variables were the treatment duration and disease activity based on Truelove and Witts criteria. Data were collected through interviews, medical records, and laboratory data, then analyzed using SPSS version 23 with a Spearman's correlation. The significance was $p < 0.05$.

RESULTS

As many as 31 subjects were included. The subjects were patients with UC diagnosed pathologically and control to the Gastroenterohepatology Outpatient Department at Dr. Soetomo Hospital who met the inclusion and exclusion criteria.

The characteristics of the study subjects were described in **Table 1**. The mean age was 46.84 ± 16.75 years (22-79 years). The majority of subjects were female (67.7%). The mean body weight was 52.84 ± 8.88 kg (39-71 kg), height 159.58 ± 7.67 cm (146-176 cm), and waist circumference 79.00 ± 4.78 cm (64-89 cm). Most subjects had normal BMI (77.4%). The average dose of 5-ASA was 1709.68 ± 668.01 mg (500-4000 mg). The duration of treatment was ≤6 months in 64.5% of subjects, and >6 months in 35.5% of subjects. The majority had increased blood pressure (51.6%), normal heart rate (67.7%), fever (61.3%), mild defecation frequency (83.9%), bloody stool (45.2%), and anemia (16.1%). Laboratory showed normal ESR (74.2%), abnormal HsCRP (93.5%), and abnormal MMP-9 (71%) levels. As many as 58.1% subjects included in moderate-severe Truelove and Witts criteria.

Table 1. The characteristic of study subjects

Variable	Value
Age (years)*	46.84 ± 16.75 (22-79)
Gender	
Male	10 (32.3)
Female	21 (67.7)
Body weight (kg)*	52.84 ± 8.88 (39-71)
Height (cm)*	159.58 ± 7.67 (146-176)
Body Mass Index (BMI)	
Normal (18.5-22.9 kg/m^2)	24 (77.4)
Underweight (<18.5 kg/m^2)	7 (22.6)
Waist circumference (cm)*	80.00 ± 4.78 (64-89)
5-ASA dose (mg)*	1500 ± 668.01 (500-4000)
Treatment duration	
≦6 months	20 (64.5)
>6 months	11 (35.5)
Blood pressure	
Normal	15 (48.4)
Increased (systolic ≧130 mmHg or diastolic ≧85 mmHg)	16 (51.6)
Heart rate	
Normal	21 (67.7)
Tachycardia (≧90 x/minute)	10 (32.3)
Fever	
Yes	19 (61.3)
No	12 (38.7)
Defecation frequency	
Mild	26 (83.9)
Severe	5 (16.1)
Bloody stool	
Yes	14 (45.2)
No	17 (54.8)
Anemia	
Yes	5 (16.1)
No	26 (83.9)
ESR	
Normal	23 (74.2)
Abnormal (≧30 mm/hour)	8 (25.8)
HsCRP	
Normal (<0.3 mg/dL)	2 (6.5)
Abnormal (≧0.3 mg/dL)	29 (93.5)
MMP-9	
Normal (169-705 ng/mL)	9 (29.0)
Abnormal (>705 ng/mL)	22 (71.0)
Truelove and Witts criteria	
Mild	13 (41.9)
Moderate - severe	18 (58.1)

*Numerical variable: Mean ± SD (min-max); Categorical variable: n (%)

Table 2. The association between LED, HsCRP, and MMP-9 level and treatment duration

Variable	Treatment duration		Spearman Correlation	OR	95%CI	P value
	≦6 months	>6 months				
LED						
Normal	13	10	-0.28	0.19	0.02-1.77	0.20
Abnormal	7	1				
HsCRP						
Normal	1	1	-0.08	0.52	0.03-9.34	1.00
Abnormal	19	10				
MMP-9						
Normal	6	3	0.03	1.14	0.22-5.87	1.00
Abnormal	14	8				

Table 3. The association between LED, HsCRP, and MMP-9 level and disease activity based on Truelove and Witts criteria.

Variable	True Love Severity		Spearman Correlation	P value
	Mild	Moderate-Severe		
LED				
Normal	13	10	0.004	0.010
Abnormal	0	8		
HsCRP				
Normal	0	2	0.23	0.50
Abnormal	13	16		
MMP-9				
Normal	4	5	0.86	1.00
Abnormal	9	13		

The association between LED, HsCRP and MMP-9 levels and treatment duration were described in **Table 2**.

Normal ESR levels were common in treatment duration of ≤6 months (13 subjects) compared to >6 months (10 subject), with a negative correlation (r = -0.28) (p = 0.20). Normal HsCRP levels were similar in treatment duration of ≤6 months and >6 months (1 subject each), with a negative correlation (r = -0.08) (p = 1.00). Normal MMP-9 levels were common in treatment duration of ≤6 months (6 subjects) compared to >6 months (3 subjects), with a very weak positive correlation (r = 0.03) (p = 1.00).

The association between ESR, HsCRP and MMP-9 levels and the Truelove and Witts criteria were described in **Table 3**.

Normal ESR levels were commonly found in mild (13 subjects) compared to moderate-severe (10 subjects). Abnormal ESR levels was most common in moderate-severe (8 subjects). The correlation between ESR levels and Truelove and Witts criteria was very weakly positive (r = 0.004) (p = 0.010). Normal HsCRP levels were not found in mild, but there were 2 subjects in moderate-severe. Abnormal HsCRP levels was commonly found in moderate-severe (16 subjects). The correlation between HsCRP levels and Truelove and Witts criteria was very weak (r = 0.23) (p = 0.50). Normal MMP-9 levels were more common in mild (4 subjects) compared to moderate-severe (5 subjects), but abnormal MMP-9 levels were common in both criteria. The correlation between MMP-9 levels and Truelove and Witts criteria was very strong (r = 0.86), but not significant (p = 1.00).

DISCUSSION

As many as 31 subjects with UC were included. In our study, the mean age was 46.84 ± 16.75 years (range 22-79 years). Most of the subjects with UC were 30 to 40 years old at diagnosis. It was higher in Asian compared to Western. Silvia et al., in southeastern Brazil showed a second peak in admission for UC in the age of 60-69 years old.[8]

There was female predominance in this study (67.7%). This was supported by a study of Betteridge et al., as many as 35,404 cases of IBD, found a female predominance among UC (RR = 1.53; 95% CI: 1.50-1.57).[9] Many studies found mostly male or equal cases for gender distribution. The enzyme polymorphism involved in insulin signal transduction increased the tendency of UC in male. However, it was refuted in a study by Spanish researchers.[8]

5-ASA is the first-line therapy for UC.[10] A study of Wang et al., and Murray et al., reported that 5-ASA was superior for maintenance of UC. 5-ASA given once daily was effective and safe compared to conventional dose for remission maintenance of UC. High-dose was safe and no adverse events.[11,12]

The mean body weight of our subjects was 52.84 ± 8.88 kg (range 39-71 kg); the height was 159.58 ± 7.67 cm (range 146-176 cm); and the median waist circumference was 90.00 (range 64-89 cm). The BMI was normal (77.4%). The higher fat mass percentage in UC related to weight gain. Consequently, BMI has adverse effect for UC progression.[8] Adiposity measurements were associated with increased risk of CD but not UC in female. Staborth-Akil et al., reported that high BMI had a better prognosis, while low BMI indicated severe disease course in UC.[13]

The clinical severity of UC can be classified based on the Truelove and Witts criteria, namely defecation frequency, bloody stools, fever, anemia, tachycardia, and ESR levels. The criteria are divided into remission, mild, moderate and severe.[14] As many as 58.1% subjects included in moderate-severe Truelove and Witts criteria. The majority had increased blood pressure (51.6%), normal heart rate (67.7%), fever (61.3%), mild defecation frequency (83.9%), bloody stool (45.2%), and anemia (16.1%). Based on laboratory examination, it was reported normal ESR levels (74.2%) and abnormal HsCRP and MMP-9 levels (93.5% and 71%, respectively). A prospective study of Jain et al., of 61 patients with severe acute colitis diagnosed by Truelove and Witts criteria, concluded that It could be used to define severe acute colitis.[15]

Our study showed a correlation between ESR levels and treatment duration (r = -0.28), so if the LED levels was normal then the treatment duration should be >6 months. Subjects with normal ESR values were 0.19 times more likely to receive treatment ≦6 months compared to >6 months (95%CI 0.02-1.77; p = 0.20). ESR levels correlation with disease activity was very weakly positive (r = 0.004) (p = 0.010). In UC, ESR plays a major role. A study by Croft et al. showed that ESR had good accuracy in assessing disease activity according to the Mayo index and degree of colectomy.[16] Yoon et al., also showed that in addition to CRP, ESR also had a moderate correlation with the degree of disease activity. However, the sensitivity and specificity of ESR are relatively lower compared to CRP.[17] Turner et al., showed that the ESR threshold for inactive disease was <23 mm/hour, for mild was 23-29 mm/hour, moderate was 30-37 mm/hour, and severe was > 37 mm/hour.[18] Osada et al., showed that ESR was related to endoscopic results and histological scores, where higher ESR levels were associated with more severe endoscopy-assessed disease activity.[19]

Our study showed a correlation between HsCRP levels and treatment period in a negative direction (r = -0.08). Subjects with normal HsCRP levels were 0.52 times more likely to receive treatment ≦ 6 months compared to >6 months (95%CI 0.03-9.34; p = 1.00). HsCRP levels correlation with disease activity was very weak (r = 0.23) (p = 0.50). HsCRP has high sensitivity and accuracy in diagnosing UC and shows the relation between clinical conditions and endoscopic activity of IBD. It has been reported that HsCRP reflects colonic mucosal inflammation, even pancolitis, better than fecal calprotectin. It has good diagnostic efficacy for acute severe UC and can replace ESR.[20,21] Studies had shown that CRP levels at the beginning of combination therapy or after 6 months of clinical remission were not statistically associated with treatment failure.[22] In addition, one-fifth of patients who did not remit after induction achieved remission within six months of continued therapy.[23] This suggests that the 6-month treatment duration is meaningful in UC disease activity.

Another study on CRP levels in UC was by Henriksen et al. This study showed that CRP levels >10 mg/l was associated with the risk of surgery within 4 years. However, CRP levels in UC were significantly lower than in CD.[24] Therefore, HsCRP levels is one of the biological markers that is closely related to the level of disease activity in UC. However, a study by Tatsumi et al., stated that the hs-CRP levels between patients with active disease and patients with remission was not significant (0.076 [0.023–0.283] vs. 0.035 [0.013–0.087] mg/dL, respectively). Hs-CRP levels showed a relatively weak correlation with clinical activity (r = 0.361).[25]

Normal and abnormal MMP-9 levels commonly found in ≦6 months treatment duration (6 and 14 subjects, respectively) in our study. Its correlation was very weak (r = 0.03). Subjects with normal MMP-9 levels were 1.14 times more likely to receive treatment for ≦6 months compared to >6 months (95%CI 0.22-5.87; p = 1.00). Normal and abnormal MMP-9 levels were more common in subjects with moderate-severe disease activity (5 subjects and 13 subjects, respectively) compared to mild. MMP-9 levels correlation with disease activity was very strong (r = 0.86) (p = 1.00).

MMP-9 is one of the metalloproteinase enzymes secreted by neutrophils. Study had shown that MMP-9 levels in the UC was increased compared to controls.[26] Faubion et al., found that MMP-9 associated with disease activity by Mayo index.[27] MMP-9 in UC acts as a proinflammatory mediator and plays a role in colonic mucosal remodeling. It catalyzes the degradation of the extracellular matrix and proteolytic enzymes

which increases inflammation. Therefore, MMP-9 expression will worsen the degree of UC.[7,28] However, the inflammation in UC due to MMP-9 was not clear, It was involved in reducing cell adhesion and calling neutrophils at the site of injury.[6]

Dysregulated MMP-9 expression in UC are implicated in the establishment and maintenance of inflammation. It is induced by proinflammatory cytokines, namely TNF-α and IL1-α. It maintains the pro-inflammatory process by releasing TNF-α and TGF-β, by potentiating IL-8, and activating IL1-β. Proteolysis of the basement membrane constituents collagen IV and laminin was done by MMP-9. Disruption of the epithelial basement membrane may result in apoptosis of epithelial cells, contributing to disruption of epithelial barrier of the colonic mucosa, which worsen the inflammation. It also facilitated the transmigration of lymphocytes and neutrophils to the site of inflammation.[29] Jakubowska et al., found an overexpression of MMP-9 in UC.[30] Piechota-Polanczyk et al., reported that increased tissue levels of cyclophilin A (CyPA) associated with higher MMP-9 and TNF-α levels in UC.[31]

Studies on MMP-9 serum levels in UC are rare. Yablecovitch et al., reported that subjects with MMP-9 levels of ≧945 ng/ml had an increased relapse rate within 24 months [AUC 0.72 [95% CI: 0.56–0.88]; hazard ratio 8.1 (95% CI 3.0–21.9, $p < 0.001$)].[32] Ghweil et al., reported that MMP-9 levels was higher in active UC compared to inactive one (11.02 ± 5.29 vs 4.01 ± 1.72 ng/ml, $p = 0.000$). MMP-9 levels and disease severity had strong positive correlation.[33] The possibility of secondary infection and antibiotic can increase the regulation of MMP-9 levels, Its abnormal levels were obtained after a treatment period of both ≦6 months and > 6 months.[34]

There were some limitations in this study. First, there were no control group. All patients in our study were patients with UC who had been diagnosed pathologically and consumed 5-ASA, so there was no comparison of inflammatory parameters of LED, HsCRP, and MMP-9 between the case and control group who were not diagnosed with 5-ASA. Another study with larger sample size and samples with undiagnosed UC as controls were needed. Second, there were no comparison of the inflammatory parameters (LED, HsCRP, and MMP-9) before and after consuming 5-ASA so that the treatment period assessment could not be significantly ascertained. Further cohort studies that followed samples before and after consuming 5-ASA were needed.

CONCLUSION

ESR, HsCRP and MMP-9 serum levels and treatment duration were not statistically significantly related. UC disease activity can be evaluated with ESR levels as an effective biomarker, when compared to MMP-9 and HsCRP levels. Further study is needed to explore the role of these biomarkers in the management of UC with a larger number of samples and comparation with non-UC subjects as control. In addition, a prospective cohort study that follows the subjects from before 5-ASA until consumed 5-ASA for the treatment duration is needed. Mayo index, UCEIS, or fecal calprotectin in assessing the severity and activity of UC can be used for further study.

REFERENCES

1. Fakhoury M, Al-Salami H, Negrulj R, Mooranian A. Inflammatory bowel disease: clinical aspects and treatments. JIR. 2014;7:113–20.
2. Mustika S, Triana N. with Ulcerative Colitis at Dr. Saiful Anwar Malang General Hospital. The Indonesian Journal of Gastroenterology, Hepatology and Digestive Endoscopy. 2016;17:16–20.
3. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–106.
4. Hirai F, Matsui T, Aoyagi K, Inoue N, Hibi T, Oshitani N, et al. VALIDITY OF ACTIVITY INDICES IN ULCERATIVE COLITIS: COMPARISON OF CLINICAL AND ENDOSCOPIC INDICES. Digestive Endoscopy. 2010;22(1):39–44.
5. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9.
6. Lin X, Li J, Zhao Q, Feng J rong, Gao Q, Nie J yan. WGCNA Reveals Key Roles of IL8 and MMP-9 in Progression of Involvement Area in Colon of Patients with Ulcerative Colitis. CURR MED SCI. 2018;38(2):252–8.
7. Marônek M, Marafini I, Gardlík R, Link R, Troncone E, Monteleone G. Metalloproteinases in Inflammatory Bowel Diseases. JIR. 2021;14:1029–41.
8. Silva BCD, Lyra AC, Rocha R, Santana GO. Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. WJG. 2014;20(28):9458–67.
9. Betteridge JD, Armbruster SP, Maydonovitch C, Veerappan GR. Inflammatory Bowel Disease Prevalence by Age, Gender, Race, and Geographic Location in the U.S. Military Health Care Population: Inflammatory Bowel Diseases. 2013;19(7):1421–7.
10. Mikami Y, Tsunoda J, Suzuki S, Mizushima I, Kiyohara H, Kanai T. Significance of 5-Aminosalicylic Acid Intolerance in the Clinical Management of Ulcerative Colitis. Digestion. 2022;104(1):58–65.
11. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in

ulcerative colitis. Cochrane IBD Group, editor. Cochrane Database of Systematic Reviews. 2016;1–92.
12. Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Gut Group, editor. Cochrane Database of Systematic Reviews. 2020;2020(8):1–130.
13. Stabroth-Akil D, Leifeld L, Pfützer R, Morgenstern J, Kruis W. The effect of body weight on the severity and clinical course of ulcerative colitis. Int J Colorectal Dis. 2015;30(2):237–42.
14. Choi CH, Moon W, Kim YS, Kim ES, Lee BI, Jung Y, et al. Second Korean guidelines for the management of ulcerative colitis. Intest Res. 2017;15(1):7–37.
15. Jain S, Kedia S, Bopanna S, Yadav DP, Goyal S, Sahni P, et al. Are Truelove and Witts criteria for diagnosing acute severe colitis relevant for the Indian population? A prospective study. Intest Res. 2018;16(1):69–74.
16. Croft A, Lord A, Radford-Smith G. Markers of Systemic Inflammation in Acute Attacks of Ulcerative Colitis: What Level of C-reactive Protein Constitutes Severe Colitis? Journal of Crohn's and Colitis. 2022;16(7):1089–96.
17. Yoon JY, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Correlations of C-reactive Protein Levels and Erythrocyte Sedimentation Rates with Endoscopic Activity Indices in Patients with Ulcerative Colitis. Dig Dis Sci. 2014;59(4):829–37.
18. Turner D, Mack DR, Hyams J, LeLeiko N, Otley A, Markowitz J, et al. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. Journal of Crohn's and Colitis. 2011;5(5):423–9.
19. Osada T, Ohkusa T, Okayasu I, Yoshida T, Hirai S, Beppu K, et al. Correlations among total colonoscopic findings, clinical symptoms, and laboratory markers in ulcerative colitis. J of Gastro and Hepatol. 2008;23(s2):S262–7.
20. Truelove SC, Witts LJ. CORTISONE IN ULCERATIVE COLITIS. British Medical Journal. (4947–1048):1955.
21. Cui J, Li X, Zhang Z, Gao H, Li J. Common laboratory blood test immune panel markers are useful for grading ulcerative colitis endoscopic severity. BMC Gastroenterol. 2022;22(540):1–10.
22. Filippi J, Laharie D, Michiels C, Flamand M, Bouguen G, Nancey S, et al. Efficacy of combination therapy for at least 6 months with thiopurines and infliximab in ulcerative colitis patients in clinical remission: a retrospective multicenter experience. Journal of Crohn's and Colitis. 2014;1–28.
23. Zezos P, Kabakchiev B, Weizman AV, Nguyen GC, Narula N, Croitoru K, et al. Ulcerative Colitis Patients Continue to Improve Over the First Six Months of Vedolizumab Treatment: 12-Month Clinical and Mucosal Healing Effectiveness. Journal of the Canadian Association of Gastroenterology. 2020;3(2):74–82.
24. Henriksen M, Jahnsen J, Lygren I, Stray N, Sauar J, Vatn MH, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut. 2008;57(11):1518–23.
25. Tatsumi Y, Kakimoto K, Hara A, Mizuta N, Numa K, Kinoshita N, et al. Biomarkers for Monitoring of Changes in Disease Activity in Ulcerative Colitis. JCM. 2023;12(22):1–10.
26. Baugh MD, Perry MJ, Hollander AP, Davies DR, Cross SS, Lobo AJ, et al. Matrix metalloproteinase levels are elevated in inflammatory bowel disease. Gastroenterology. 1999;117(4):814–22.
27. Faubion WA, Fletcher JG, O'Byrne S, Feagan BG, De Villiers WJ, Salzberg B, et al. Emerging BiomARKers in Inflammatory Bowel Disease (EMBARK) Study Identifies Fecal Calprotectin, Serum MMP9, and Serum IL-22 as a Novel Combination of Biomarkers for Crohn's Disease Activity: Role of Cross-Sectional Imaging. American Journal of Gastroenterology. 2013;108(12):1891–900.
28. Bai X, Bai G, Tang L, Liu L, Li Y, Jiang W. Changes in MMP-2, MMP-9, inflammation, blood coagulation and intestinal mucosal permeability in patients with active ulcerative colitis. Exp Ther Med. 2020;20(1):269–74.
29. Marshall DC, Lyman SK, McCauley S, Kovalenko M, Spangler R, Liu C, et al. Selective Allosteric Inhibition of MMP9 Is Efficacious in Preclinical Models of Ulcerative Colitis and Colorectal Cancer. Cominelli F, editor. PLoS ONE. 2015;10(5):e0127063.
30. Jakubowska K, Pryczynicz A, Iwanowicz P, Niewiński A, Maciorkowska E, Hapanowicz J, et al. Expressions of Matrix Metalloproteinases (MMP-2, MMP-7, and MMP-9) and Their Inhibitors (TIMP-1, TIMP-2) in Inflammatory Bowel Diseases. Gastroenterology Research and Practice. 2016;2016:1–7.
31. Piechota-Polanczyk A, Włodarczyk M, Sobolewska-Włodarczyk A, Jonakowski M, Pilarczyk A, Stec-Michalska K, et al. Serum Cyclophilin A Correlates with Increased Tissue MMP-9 in Patients with Ulcerative Colitis, but Not with Crohn's Disease. Dig Dis Sci. 2017;62(6):1511–7.
32. Yablecovitch D, Kopylov U, Lahat A, Amitai MM, Klang E, Ben-Ami Shor D, et al. Serum MMP-9: a novel biomarker for prediction of clinical relapse in patients with quiescent Crohn's disease, a *post hoc* analysis. Therap Adv Gastroenterol. 2019;12:1–11.
33. Ghweil A, Khodeary A, Aziz SP. Diagnostic Value of Fecal Calprotectin and Serum MMP-9 in Diagnosing Disease Activity of Ulcerative Colitis. OJGas. 2018;08(06):234–44.
34. O'Sullivan S, Gilmer JF, Medina C. Matrix Metalloproteinases in Inflammatory Bowel Disease: An Update. Oral HB, editor. Mediators of Inflammation. 2015;2015:1–19.