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Serum NGAL and S100A12 as Biomarkers of Active Disease in Ulcerative Colitis

Ülseratif Kolitte Aktif Hastalığın biyobelirteçleri olarak serum NGAL ve S100A12

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ABSTRACT

Aim: To investigate the potential use of serum neutrophil gelatinase-associated lipocalin (NGAL) and S100A12 (S100 calcium-binding protein A12) as biomarkers for determining disease activity in ulcerative colitis (UC) within the same study.

Materials and Methods: The study included individuals from the active (n=34) and remission (n=34) periods of the same UC patients, as well as a control group (n=31). Venous blood samples were collected from patients with clinically and endoscopically diagnosed UC and from the control group to analyze NGAL and S100A12 levels, in addition to routine laboratory tests. All demographic and clinical variables were compared between the groups.

Results: Patients with active ulcerative colitis exhibited markedly higher serum NGAL and S100A12 concentrations than those in remission or the control group ($p = 0.001$ and $p < 0.001$, respectively). In the ROC analysis performed to detect active UC, NGAL and S100A12 showed high sensitivity and specificity at their optimal cut-off values ($p<0.001$). In the multinomial logistic regression analysis with the control group as the reference, both NGAL and S100A12 levels in the active group, and S100A12 levels in the remission group, remained significantly associated with active disease in both unadjusted and adjusted models. Each unit increase in these markers significantly increased the likelihood of active disease ($p<0.05$ for all comparisons).

Conclusions: In this study, serum NGAL and S100A12 concentrations were markedly elevated in the active UC group relative to the remission and control groups. Larger studies are needed.

Keywords: Ulcerative colitis, NGAL, S100A12

ÖZ

Amaç: *Bu çalışmada, ülseratif kolit (ÜK) hastalarında serum nötrofil jelatinaz ilişkili lipokalin (NGAL) ve S100A12 (S100 kalsiyum bağlayıcı protein A12) düzeylerinin hastalık aktivitesinin belirlenmesinde biyobelirteç olarak kullanılabilirliğinin aynı çalışma kapsamında araştırılması amaçlandı.*

Gereç ve Yöntem: *Çalışmaya, aynı ÜK hastalarının aktif (n=34) ve remisyon (n=34) dönemlerinde değerlendirilen bireyler ile kontrol grubu (n=31) dahil edildi. Klinik ve endoskopik olarak ÜK tanısı alan hastalardan ve kontrol grubundan venöz kan örnekleri alınarak NGAL ve S100A12 düzeyleri ile rutin laboratuvar parametreleri analiz edildi. Tüm demografik ve klinik değişkenler gruplar arasında karşılaştırıldı.*

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Bulgular: *Aktif ülseratif kolit hastalarında serum NGAL ve S100A12 düzeyleri, remisyon dönemindeki hastalara ve kontrol grubuna kıyasla belirgin şekilde daha yüksek bulundu (sırasıyla p = 0.001 ve p <0.001). Aktif ÜK'yı saptamak amacıyla yapılan ROC analizinde, NGAL ve S100A12 en uygun kesim değerlerinde yüksek duyarlılık ve özgüllük gösterdi (p <0.001). Kontrol grubu referans alınarak yapılan multinomiyal lojistik regresyon analizinde hem NGAL hem de S100A12 düzeyleri aktif grupta; S100A12 düzeyleri ise remisyon grubunda, ayarlanmamış ve ayarlanmış modellerde aktif hastalık varlığı ile anlamlı şekilde ilişkili kaldı. Bu belirteçlerdeki her bir birimlik artış aktif hastalık olasılığını anlamlı ölçüde artırdı (tüm karşılaştırmalar için p <0.05).*

Sonuç: *Bu çalışmada, aktif ÜK grubunda serum NGAL ve S100A12 düzeylerinin remisyon ve kontrol gruplarına kıyasla belirgin şekilde yüksek olduğu gösterilmiştir. Daha geniş kapsamlı çalışmalara ihtiyaç vardır.*

Anahtar Sözcükler: Ülseratif kolit, NGAL, S100A12

INTRODUCTION

Inflammatory bowel disease (IBD) is a persistent intestinal inflammatory condition of unclear etiology, characterized by alternating periods of remission and relapse, encompassing two principal forms: ulcerative colitis (UC) and Crohn's disease (CD). UC is a chronic, recurrent disease that causes diffuse inflammation of the intestinal tract and involves only the colonic mucosa. Inflammation usually begins in the rectum, progresses proximally, and may include part or all of the colon (1-3). The incidence and prevalence of the disease vary according to factors such as regional and ethnic structure, socioeconomic status, age, and sex. Although the etiology of IBD has not been fully elucidated, environmental, genetic, and immunological factors are thought to play essential roles (4).

Intestinal inflammation in IBD leads to increased acute-phase reactants and leukocyte migration to the site of inflammation. Consequently, many proinflammatory proteins formed in the environment can be detected in serum and stool (5). As part of the acute-phase response, an increase in leukocyte numbers may be observed. Increased acute-phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocyte and platelet counts, fibrinogen, and ferritin serve as crucial indicators of disease activity (6).

NGAL, also referred to as lipocalin-2, is a protein secreted by specific cells in the body under stress. It is expressed at low levels in the kidney, prostate, endothelial cells, hepatic cells, cardiomyocytes, respiratory and gastrointestinal epithelium, inflamed intestinal epithelium, postpartum uterine tissue, and activated neutrophils (7-9). NGAL can be considered an acute-phase protein. Clinical research has shown increased serum NGAL concentrations in several inflammation-associated conditions (7). Earlier research has shown that serum NGAL concentrations rise two- to threefold during active IBD compared with remission, effectively differentiating the active disease stage (10). Komosińska-Vassev K et al. reported that serum NGAL levels were elevated in IBD patients compared with healthy individuals, with even higher values observed in those with CD than in controls (11). Another investigation likewise observed increased serum NGAL concentrations in patients with active IBD (12). Compared with other markers such as CRP, ESR, or fecal calprotectin, NGAL has been shown to be a stronger statistical indicator in predicting IBD activity (13).

S100A12, or calgranulin C, is a calcium-binding proinflammatory molecule classified within the S100 protein family (14). S100A12 is part of the S100 family of EF-hand calcium-binding proteins involved in multiple intracellular and extracellular functions. More than twenty S100 proteins have been identified, many forming dimers that play roles in Ca^{2+} signaling and regulate processes such as calcium balance, energy metabolism, cell growth, and differentiation (15, 16). In humans, the gene expression of S100A12 is almost entirely restricted to neutrophil granulocytes. Although monocytes can express it, expression levels are much lower than in neutrophils (17). S100A12 has been reported to be an important marker for many inflammatory diseases, such as arthritis, asthma, cystic fibrosis, and inflammatory bowel disease (8). S100A12 levels are markedly elevated in chronic active IBD and play a significant role in the disease's pathogenesis (18).

Determining disease activity in UC is crucial for predicting prognosis and guiding treatment decisions. Numerous studies to date have sought to identify an ideal disease marker. In recent

years, noninvasive, simple, and rapid laboratory markers have been investigated to evaluate disease activity and treatment response. For this purpose, many clinical activity indices and noninvasive markers have been used; however, these have yielded only indirect findings in assessing disease activity. Studies have shown that NGAL and S100A12 are elevated in UC patients. These two markers have been examined separately in previous studies. Our aim, which differs from earlier work, is to evaluate these two markers together, investigate their relationship in both the active and remission phases within the same patient group, and compare them with healthy subjects.

MATERIALS AND METHODS

Study design, sample size, and population

A total of 34 patients diagnosed clinically and endoscopically with ulcerative colitis (UC) according to endoscopic findings and Truelove–Witts score, who presented to the Gastroenterology outpatient clinic and Gastroenterology Endoscopy Unit of Canakkale Onsekiz Mart University Hospital during 15 months and were in the active phase of their disease, were included in the study. The same patients were also evaluated during their remission phase after a 3–6-month follow-up period. The healthy control group consisted of 31 individuals without any chronic or acute disease who underwent colonoscopy for cancer screening or check-up purposes.

Inclusion criteria:

- Age ≥18 years
- No additional acute or chronic disease
- eGFR >60 mL/min/1.73 m²
- Diagnosed UC patients with both active and remission phases confirmed clinically and endoscopically
- Written informed consent was obtained

Exclusion criteria:

- Age<18 years
- Lactating and pregnant women
- Presence of additional acute or chronic diseases
- eGFR <60 mL/min/1.73 m²
- Patients without a confirmed diagnosis of UC or without clinically and endoscopically verified active and remission phases
- Failure to obtain written informed consent

General characteristics and data collection

Demographic characteristics, disease localization, disease duration, treatment, laboratory parameters, and endoscopic and clinical disease activity indices of the patients were prospectively recorded in pre-prepared data files. Clinical activity indices during the active phase were calculated using the Truelove–Witts score. In addition to routine laboratory tests, 10 mL of venous blood was collected from patients in the active and remission phases of UC and from control participants to analyze NGAL and S100A12 levels. Venous blood samples were spun at 3000 rpm for 10 minutes to separate plasma and serum. The obtained serum samples were stored in Eppendorf tubes at −40 °C in the deep freezer of the gastroenterology endoscopy unit until all samples were collected.

Measurement of serum NGAL and S100A12 levels

Serum NGAL and S100A12 levels were determined using the enzyme-linked immunosorbent assay (ELISA). Measurements were performed with commercially available sandwich-type ELISA kits (ELK Biotechnology, Wuhan, China). According to the manufacturer, detection limits were 0.065 ng/mL for NGAL and 30 pg/mL for S100A12. The intra-assay and inter-assay coefficients of variation were below 8% and 10%, respectively. All serum specimens were kept at −40 °C prior to analysis, with repeated freeze–thaw cycles strictly avoided. According to the manufacturer's recommendations, kit reagents remain stable for 6 months at 4 °C and for up to 12 months at −20 °C. All analyses were performed using a Multiskan FC microplate reader (Thermo Scientific, Finland).

Ethical approval

The study received approval from the Ethics Committee of Çanakkale Onsekiz Mart University Faculty of Medicine (Decision No: 03-02; Date: 12.02.2020; Approval Code: 2011-KAEK-27/2020-E.2000005060).

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The normality of numerical data was tested with the Kolmogorov–Smirnov test. Variables with normal distribution were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median (minimum–maximum). Categorical variables were presented as frequencies and percentages. Independent group comparisons were made using the Student's t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Correlations between NGAL, S100A12, and other variables were assessed with Spearman's rank correlation coefficient. Multinomial logistic regression was performed to identify independent predictors. Receiver operating characteristic (ROC) analysis was employed to distinguish patients in the active phase of UC. A p-value below 0.05 was regarded as statistically significant.

G*Power software version 3.1.9.4 was used to do the power analysis. To assess the difference between two independent groups, the study used the sample sizes of the UC and control groups as well as the reported between-group changes in serum NGAL and S100A12 levels. As a result, 97% for NGAL and 100% for S100A12 were determined to be the achieved statistical power.

RESULTS

The mean age was 47.68 ± 15.55 years in UC patients and 52.45 ± 12.51 years in controls, with no significant difference ($p = 0.18$). Males accounted for 61.8% of UC patients and 32.3% of controls ($p = 0.017$). There was no significant difference in smoking status between the groups ($p = 0.865$). Demographic data are summarized in Table-1.

All patients were receiving medical therapy with mesalazine or mesalazine plus immunosuppressive agents. The median disease duration was 16 (1–104) months. Based on the Truelove–Witts classification, disease activity was mild, moderate, or severe; however, no significant differences in NGAL or S100A12 levels were observed among the groups (all $p > 0.05$).

In laboratory findings, significant differences were observed between groups in WBC, neutrophil count, creatinine, CRP, ESR, NGAL, and S100A12 levels (all $p < 0.05$). Post-hoc analyses of parameters with significant differences revealed that WBC, neutrophil count, creatinine, CRP, and ESR differed between the active UC patients and control groups; however, no significant difference was observed between the active–remission and control–remission groups. For NGAL, post-hoc analyses indicated significant differences between the active–control ($p < 0.05$) and active–remission groups ($p < 0.05$), but not between the remission and control groups ($p > 0.05$). For S100A12, post hoc analyses demonstrated significant differences across all three comparisons (active–control, active–remission, and remission–control) (all $p < 0.05$). No significant differences were observed in the other parameters. Laboratory results and post-hoc analyses are summarized in Table-2.

NGAL levels were higher in the active phase than in the remission and control groups. During remission, NGAL levels were comparable to those in the control group. S100A12 concentrations were higher in the active phase than in the remission and control groups and remained elevated during remission compared with controls. Figure-1 illustrates the box plot of NGAL and S100A12 distributions in active and remission UC phases and in the control group.

Compared with controls, the optimal cutoff for detecting active UC was 133 ng/mL for NGAL, with 70.6% sensitivity and 61.5% specificity. For S100A12, a threshold of 1335 pg/mL yielded 97.1% sensitivity and 83.1% specificity. The WBC cutoff of 7.5 × 10^3/mL yielded 70.6% sensitivity and 55.4% specificity, while a CRP level of 0.3 mg/dL yielded 73.5% sensitivity and 38.5% specificity. Ferritin showed a cutoff of 61 ng/mL, with 58.8% sensitivity and 53.8% specificity. Table-3 summarizes the diagnostic performance of serum NGAL, S100A12, and other inflammatory markers for active UC, and Figure-2 presents the corresponding ROC curve.

In a multinomial logistic regression analysis with the control group as the reference, each unit increase in NGAL level in active patients significantly increased the likelihood of active disease (crude OR = 1.027, 95% CI: 1.010–1.044, $p = 0.002$). This relationship remained significant after adjustment for age, sex, creatinine, WBC, and CRP (adjusted OR = 1.032, 95% CI: 1.012–1.053, $p = 0.002$). NGAL levels did not differ significantly between the remission and control groups ($p = 0.991$). Regarding S100A12, each unit increase in S100A12 level in active patients was

strongly associated with disease activity compared with the control group (crude OR = 1.008, p < 0.001). This relationship remained significant in the adjusted model as well (adjusted OR = 1.008, p < 0.001). In the remission group, each unit increase in S100A12 levels compared to controls was also significantly associated with a higher probability of active disease (crude OR = 1.003, p = 0.002). This relationship persisted as statistically significant after adjustment (adjusted OR = 1.003, p = 0.004). The results of the multinomial logistic regression analysis examining the relationships among NGAL, S100A12, and disease activity are presented in Table-4**.**

NGAL was positively and significantly correlated with S100A12**,** disease duration, and ESR, whereas no significant associations were identified with WBC, neutrophil count, albumin, or creatinine (p > 0.05). S100A12 showed a significant positive correlation with disease duration, WBC, neutrophil count, albumin, and creatinine, whereas the correlation with ESR was positive but not statistically significant (p = 0.088). The results of Spearman correlation analyses between NGAL and S100A12 levels and clinical/laboratory variables are presented in Table-5.

Table-1. Demographic characteristics of individuals included in the study

Parameters		**Ulcerative colitis n=34**	**Control n=31**	**p-value**
Sex, Male n (%)		21 (61.8)	10 (32.3)	0.017
Age, mean ± standard deviation		47.68 ±15.55	52.45 ±12.51	0.180
Smoking status, n (%)	Non-smoker	14 (41.2)	14 (45.2)	
	Current smoker	12 (35.3)	9 (29.0)	
	Former smoker	8 (23.5)	8 (25.8)	0.865

p-value: statistical significance

Table-2. Laboratory data of the groups included in the study and the differences between them

Parameters	**Control n=31**	**Active n=34**	**Remission n=34**	**p-value**
WBC (x1000/mL)	6.8 (4.9-10.1) [a]	8.85 (4.1-17.3) [b]	7.75 (4-14.3) [a, b]	0.009
Hemoglobin (g/dL)	13.27±2.05	13.59±1.89	14.01±1.61	0.321
Platelet (x1000/mL)	257 (125-399)	318 (169-938)	260 (171-506)	0.112
Neutrophil (x1000/mL)	3.8 (2.3-6.7) [a]	4.55 (0.8-13.3) [b]	4.7 (2-9.2) [a,b]	0.025
Lymphocyte (x1000/mL)	2.1 (0.9-4.1)	2.4 (0.9-5.7)	2.05 (1-4.2)	0.163
MPV (fL)	8.4 (6.5-9.7)	8.45 (4.6-9.9)	8.3 (6.7-9.6)	0.587
Glucose (mg/dL)	99 (82.6-169)	100.15 (82.2-372)	98 (72.4-305.1)	0.528
Albumin (g/dL)	4.39±0.32	4.53±0.53	4.52±0.41	0.143
Urea (mg/dL)	23 (14-40.1)	24.95 (12.50-63.1)	23.25 (8.1-64)	0.567
Creatinine (mg/dL)	0.73 (0.48-1.12) [a]	0.90 (0.58-1.3) [b]	0.82 (0.1-1.82) [a, b]	0.012
AST (U/L)	18.3 (12-30)	17.4 (10.8-67.3)	17.15 (10.09-47)	0.302
ALT (U/L)	17.5 (6.7-146.5)	14.9 (6.4-76.6)	17 (6-57)	0.893
CRP (mg/dL)	0.4 (0.1-10.10) [a]	0.64 (0.1-13.2) [b]	0.33 (0.1-3.63) [a, b]	0.033
Sedimentation (mm/h)	12 (2-44) [a]	21.5 (5-118) [b]	15 (3-59) [a, b]	0.005
Ferritin (ng/mL)	65 (3-90)	71.82 (5.29-418)	48 (5.99-220)	0.141
NGAL (ng/mL)	123.88±22.25 [a]	152.26±36.48 [b]	123.97±37.42 [a]	0.001
S100A12 (pg/mL)	872.89 (562.49-1547.75) [a]	2531.14 (1245.71-4163.01) [b]	1135 (503.72-2340.17) [c]	<0.001

WBC: White Blood Cells; MPV: Mean Platelet Volume; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase. NGAL: Neutrophil gelatinase-associated lipocalin; S100A12: S100 calcium binding protein A12; p-value: statistical significance (p<0.05 was accepted as statistically significant)

“a, b, c” superscripts refer to the statistically significant differences in post-hoc analyses between groups. The same letters indicate there were no significant differences (p<0.05).

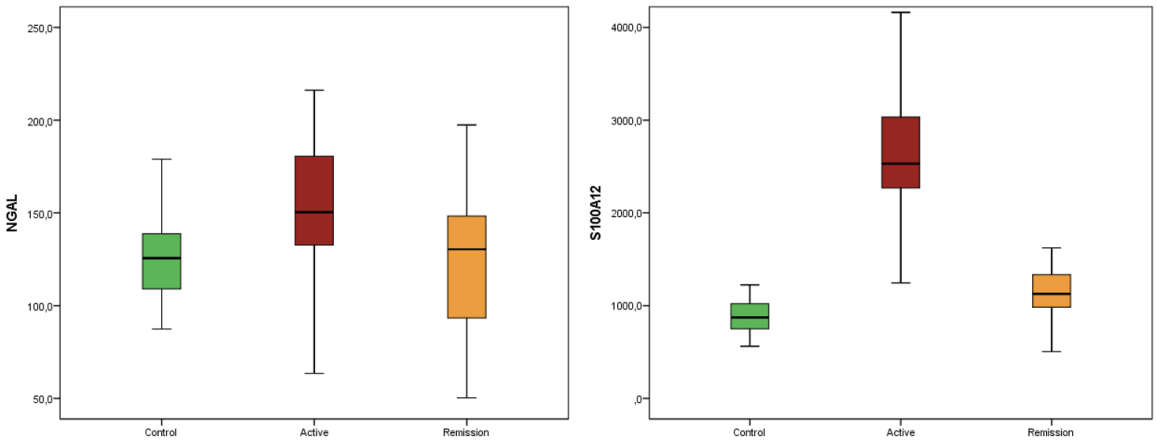

Figure-1. Box Plot graph of the distribution of serum NGAL and S100A12 levels in active, remission UC patients, and the control group.

Table-3. The role of serum NGAL, S100A12, and other inflammatory markers in predicting active-stage UC (compared to the control group)

Parameters	cut-off	AUC	CIs of AUCs	p-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC (x1000/mL)	7.5	0.671	0.601-0.829	0.005	70.6	55.4	45.3	43.5
CRP (mg/dL)	0.30	0.660	0.536-0.777	0.009	73.5	38.5	38.5	42.4
Ferritin (ng/mL)	61	0.611	0.473-0.722	0.071	58.8	53.8	40.0	71.4
NGAL (ng/mL)	133	0.725	0.635-0.855	< 0.001	70.6	61.5	49.0	80.0
S100A12 (pg/mL)	1335	0.980	0.939-1.000	< 0.001	97.1	83.1	75.0	98.2

NGAL: Neutrophil gelatinase-associated lipocalin; S100A12: S100 calcium binding protein A12; WBC: White Blood Cells; CRP: C- reactive protein; p-value: statistical significance; PPV: positive predictive value; NPV: negative predictive value; AUC: Area under the curve

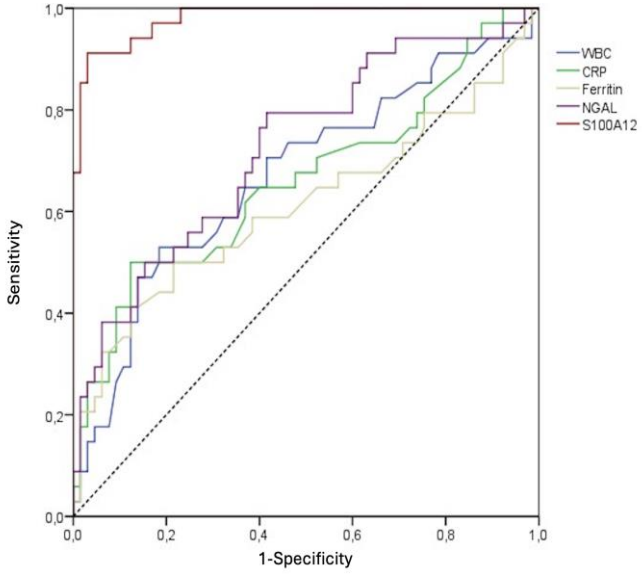

Figure-2. The role of serum NGAL, S100A12, and other inflammatory markers in predicting active-stage UC compared to the healthy control group (the ROC curve analysis results).

Table-4. Multinomial logistic regression analysis of the relationship between NGAL and S100A12 and disease activity

Parameters	OR	95% CI	p-value
For NGAL levels			
Crude			
• Control	reference	-	-
• Active	1.027	1.010-1.044	0.002
• Remission	1.000	0.985-1.015	0.991
Adjusted			
• Control	reference	-	-
• Active	1.032	1.012-1.053	0.002
• Remission	1.001	0.985-1.018	0.879
For S100A12 levels			
Crude			
• Control	reference	-	-
• Active	1.008	1.005-1.011	<0.001
• Remission	1.003	1.001-1.006	0.002
Adjusted			
• Control	reference	-	-
• Active	1.008	1.005-1.012	<0.001
• Remission	1.003	1.001-1.006	0.004

NGAL: Neutrophil gelatinase-associated lipocalin; S100A12: S100 calcium binding protein A12; OR: Odds ratio; CI: Confidence interval; p-value level of statistical significance
The models were adjusted for age, sex, WBC, creatinine, and CRP. Variables showing multicollinearity were excluded from the models. The control group was considered the reference in the regression models.

Table-5. Spearman's correlation analysis between clinical and laboratory data of NGAL and S100A12 levels

Parameters	NGAL ρ (p)	SA100A12 ρ (p)
S100A12 (pg/mL)	0.250 (0.013)	-
NGAL (ng/mL)	-	0.250 (0.013)
Disease duration, months	0.347 (0.005)	0.809 (<0.001)
Sedimentation, mm/h	0.203 (0.044)	0.172 (0.088)
WBC (x1000/mL)	0.140 (0.891)	0.268 (0.007)
Neutrophil (x1000/mL)	0.053 (0.605)	0.204 (0.043)
Albumin, mg/dL	0.192 (0.057)	0.224 (0.026)
Creatinine, mg/dL	0.045 (0.660)	0.209 (0.038)

ρ: Spearman's correlation coefficient; p: statistical significance (p<0.05 was accepted as statistically significant); NGAL: Neutrophil gelatinase-associated lipocalin; S100A12: S100 calcium binding protein A12; WBC: White Blood Cells

DISCUSSION

In this study, serum NGAL and S100A12 concentrations were markedly elevated in active UC patients compared with those in remission and the control group. Furthermore, S100A12 levels during the remission phase of UC remained notably elevated relative to the control group. These findings indicate that serum NGAL and S100A12 levels could serve as reliable noninvasive biomarkers for detecting disease activation in UC.

The diagnosis of IBD is challenging and necessitates a comprehensive evaluation based on clinical findings, endoscopic and radiologic assessments, pathological results, and differentiation from other gastrointestinal disorders presenting with similar symptoms. However, existing diagnostic approaches are constrained by prolonged processing times, high costs, and invasiveness, limiting early detection and screening for IBD (19, 20). Thus, an accessible, cost-effective, and practical serum biomarker is crucial for early diagnosis and disease follow-up.

As a major component of neutrophil granule proteins, increased NGAL expression may reflect typical pathological changes in IBD, such as neutrophil infiltration and activation in the intestinal mucosa (21). A recent study also reported significantly higher median serum NGAL levels in UC patients than in healthy controls (22). Nooh et al. found markedly higher serum NGAL levels in active UC and CD patients than in inactive CD and

healthy controls (23). In comparisons between active IBD and healthy controls, the AUC values were 0.987 (95% CI: 0.97–1.0) for fecal NGAL and 0.980 (95% CI: 0.95–1.0) for calprotectin. At cutoff levels of 0.81 mg/kg and 50 mg/kg, both achieved 94.7% sensitivity and 95.7% specificity (24).

Oikonomou et al. reported that serum NGAL, at a cutoff value of 97 ng/mL, outperformed ESR and CRP in differentiating active from inactive IBD (12). Yeşil et al. reported that serum NGAL with a cutoff of 129 ng/mL had 76.1% sensitivity and 60.9% specificity as the optimal threshold for differentiating IBD patients from controls (25). In our study, serum NGAL had a cutoff value of 133 ng/mL, yielding a sensitivity of 70.6% and specificity of 61.5%. Compared with other inflammation-related markers such as ferritin, WBC, and CRP, NGAL demonstrated higher specificity, equal sensitivity to WBC, and greater sensitivity than CRP and ferritin. This indicates that NGAL could serve as a noninvasive biomarker for identifying active UC.

S100A12, released from activated neutrophils, contributes to inflammation by activating the receptor for advanced glycation end products (RAGE) (26). In UC, enhanced neutrophil migration into the intestinal mucosa may result in increased S100A12 expression at the site of inflammation. Moreover, S100A12 enhances proinflammatory cytokine secretion and monocyte migration, leading to further S100A12 release and a self-sustaining inflammatory loop (27). Foell et al. observed increased serum S100A12 levels in UC patients (18). Thus, identifying S100A12 as a potential biomarker for UC could be key to developing new diagnostic and therapeutic strategies. Another study likewise reported significantly higher serum S100A12 levels in UC than in healthy controls, with a strong correlation with the Mayo score before and after treatment (28). Fecal S100A12 levels were elevated in patients with active IBD compared to healthy controls and those with IBS, distinguishing active IBD from healthy individuals with 86% sensitivity and 100% specificity (29). Another study demonstrated that serum S100A12 levels were higher in the active phase than in remission and control groups, and also higher in remission than in controls (30). In this study, serum S100A12 levels were markedly higher in active UC patients than in those in remission and controls and stayed elevated during remission compared with controls. At a cutoff of 1335 pg/mL, serum S100A12 demonstrated 97.1% sensitivity and 83.1% specificity, with higher diagnostic performance than other inflammatory markers, such as WBC, CRP, and ferritin. These findings support and are consistent with results reported in the literature. Although serum S100A12 demonstrated high diagnostic performance in the present study, external validation in larger, multicenter cohorts is required before its routine clinical implementation.

The strengths of our study include the simultaneous evaluation of NGAL and S100A12 in the same research, its prospective design, and the inclusion of patients in both active and remission phases, as well as a healthy control group. The study limitations were its small sample size, single-center design, lack of endoscopic scoring in UC patients, and absence of fecal or tissue assessments for NGAL and S100A12. The strong findings from our study, with high specificity, should be further validated by larger, multicenter, prospective studies involving more patients and controls, and by incorporating analyses of fecal and tissue expression of NGAL and S100A12. The absence of an a priori power analysis can be considered a limitation of the study. Nevertheless, the high-power values obtained from the power analysis conducted after the study based on the study results enhance the reliability of the findings.

Both markers were strongly correlated with UC disease activity, and S100A12 exhibited particularly high sensitivity and specificity. These results indicate that NGAL and S100A12 may serve as useful noninvasive biomarkers for evaluating UC activity. Larger studies are needed to confirm whether these markers can be used as noninvasive tests for monitoring UC prognosis and treatment response.

CONCLUSION

Both markers were strongly correlated with UC disease activity, and S100A12 exhibited particularly high sensitivity and specificity. These results indicate that NGAL and S100A12 may serve as useful noninvasive biomarkers for evaluating UC activity. Larger studies are needed to confirm whether these markers can be used as noninvasive tests for monitoring UC prognosis and treatment response.

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References

1. Berry SK, Melmed GY. Quality indicators in inflammatory bowel disease. Intestinal research. 2018;16(1):43-7.
2. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113(4):481-517.
3. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. Gastroenterology. 2004;126(6):1518-32.
4. Satsangi J, Silverberg M, Vermeire S, Colombel J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-53.
5. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. The Lancet. 2017;390(10114):2769-78.
6. Ince MN, Elliott DE. Effective use of the laboratory in the management of patients with inflammatory bowel diseases. Gastroenterol Clin North. 2019;48(2):237-58.
7. Borkham-Kamphorst E, Drews F, Weiskirchen R. Induction of lipocalin-2 expression in acute and chronic experimental liver injury moderated by pro-inflammatory cytokines interleukin-1β through nuclear factor-κB activation. Liver International. 2011;31(5):656-65.
8. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol.. 2003;14(10):2534-43.
9. Yndestad A, Landrø L, Ueland T, Dahl CP, Flo TH, Vinge LE, et al. Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. Eur Heart J.. 2009;30(10):1229-36.
10. Korkmaz H, Asil M, Temel T, Öztürk B, Kebapcilar L. Evaluation of serum neutrophil gelatinase-associated lipocalin (NGAL), asymmetricdimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) levels, and theirrelations with disease type and activity in inflammatory bowel diseases. Turk J Med Sci.. 2021;51(5):2403-12.
11. Komosinska-Vassev K, Kałużna A, Jura-Półtorak A, Derkacz A, Olczyk K. Circulating profile of ECM-related proteins as diagnostic markers in inflammatory bowel diseases. J Clin Med.. 2022;11(19):5618.
12. Oikonomou K, Kapsoritakis A, Theodoridou C, Karangelis D, Germenis A, Stefanidis I, et al. Neutrophil gelatinase-associated lipocalin (NGAL) in inflammatory bowel disease: association with pathophysiology of inflammation, established markers, and disease activity. J Gastroenterol.. 2012;47(5):519-30.
13. Abozeid F, Ali K, Bahgat M, Maher M, Borg AM. Assessing the activity of Inflammatory Bowel Disease using the serum marker: Neutrophil Gelatinase Associated Lipocalin (NGAL). Mansoura Medical Journal. 2023;53(1):2.
14. Meijer B, Gearry R, Day A. The role of S100A12 as a systemic marker of inflammation. Int J Inflam.. 2012;2012(1):907078.
15. Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, J Weber D, et al. Functions of S100 proteins. Curr Mol Med. 2013;13(1):24-57.
16. Heizmann CW, Fritz G, Schafer B. S100 proteins: structure, functions and pathology. Front Biosci (Landmark Ed)) 2002;7(1):1356-68.
17. Guignard F, Mauel J, Markert M. Identification and characterization of a novel human neutrophil protein related to the S100 family. Biochem J. 1995;309(2):395-401.

18. Foell D, Kucharzik T, Kraft M, Vogl T, Sorg C, Domschke W, et al. Neutrophil derived human S100A12 (EN-RAGE) is strongly expressed during chronic active inflammatory bowel disease. Gut. 2003;52(6):847-53.
19. Levy I, Gralnek IM. Complications of diagnostic colonoscopy, upper endoscopy, and enteroscopy. Best Pract Res Clin Gastroenterol. 2016;30(5):705-18.
20. Horiuchi I, Horiuchi K, Horiuchi A, Umemura T. Serum leucine-rich α2 glycoprotein could be a useful biomarker to differentiate patients with normal colonic mucosa from those with inflammatory bowel disease or other forms of colitis. J Clin Med. 2024;13(10):2957.
21. Aghsaeifard Z, Alizadeh R, Bagheri N. Association between neutrophil gelatinase-associated lipocalin (NGAL) and iron profile in chronic renal disease. Arch Physiol Biochem.2022;128(3):703-7.
22. Elshereef HK, Helbawi FM, Mahmoud ME, Abdelwahab HM. Serum neutrophil gelatinase-associated lipocalin as promising diagnostic marker and a predictor of activity of ulcerative colitis patients: single center study. Egypt J Haematol.. 2024;49(1):108-14.
23. Nooh M, Mohammed H, Taiel S, El Hagary H. Study of serum neutrophil gelatinase-associated lipocalin level in inflammatory bowel disease patients. Menoufia Med J. 2018;31(2):600-.
24. Thorsvik S, Damås JK, Granlund Av, Flo TH, Bergh K, Østvik AE, et al. Fecal neutrophil gelatinase-associated lipocalin as a biomarker for inflammatory bowel disease. J Gastroenterol Hepatol.2017;32(1):128-35.
25. Yeşil A, Gönen C, Şenateş E, Paker N, Gökden Y, Koçhan K, et al. Relationship between neutrophil gelatinase-associated lipocalin (NGAL) levels and inflammatory bowel disease type and activity. Dig Dis Sci. 2013;58(9):2587-93.
26. Hofmann MA, Drury S, Fu C, Qu W, Taguchi A, Lu Y, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell. 1999;97(7):889-901.
27. Kaur A, Goggolidou P. Ulcerative colitis: understanding its cellular pathology could provide insights into novel therapies. Inflamm (Lond). 2020;17(1):15.
28. Kałużna A, Jura-Półtorak A, Derkacz A, Jaruszowiec J, Olczyk K, Komosinska-Vassev K. Circulating profiles of serum proguanylin, S100A12 protein and Pentraxin 3 as diagnostic markers of ulcerative colitis. J Clin Med. 2023;12(13):4339.
29. Kaiser T, Langhorst J, Wittkowski H, Becker K, Friedrich AW, Rueffer A, et al. Faecal S100A12 as a non-invasive marker distinguishing inflammatory bowel disease from irritable bowel syndrome. Gut. 2007;56(12):1706-13.
30. Zhang Q, Zuo Y, Xu M. The correlation of serum vaspin, S100A12 and PCT levels with the severity of ulcerative colitis and its clinical significance. Am J Transl Res. 2021;13(7):7914.