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Correlation between Neutrophil Gelatinase-Associated Lipocalin and Endoscopic, Histopathologic and Clinical Activities of Ulcerative Colitis

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Authors' contributions

This work was carried out in collaboration among all authors. Author MGF designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors WSM and SEE managed the analyses of the study and the literature searches. Author HAM performed the laboratory investigation done during the study. Author EAH performed the histopathological analysis done during the study. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Detection of activity of ulcerative colitis (UC) is vital for predicting treatment outcome. The assessment depends on clinical, serologic, and endoscopic findings. One of the noninvasive biomarkers for disease activity detection is serum Neutrophil Gelatinase-Associated Lipocalin (NGAL).
Aim: To assess the relationship between NGAL and endoscopic, histopathologic and clinical activity of UC.
Methods: This study was conducted on 50 cases with definitive diagnosis of UC and 15 cases with normal colonoscopy examination as controls**.** UC cases were considered active if Geobes score was ≥3.1. Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)

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and liver and kidney function tests were done. Serum NGAL was estimated using ELISA technique.

Results: UC cases were classified into active group (n = 36) and inactive group (n = 14). In active UC cases, median value (IQR) of serum NGAL was significantly increased (101.15 (67.53 – 156.40) ng/mL) compared to inactive cases (63.35 (60.98–65.20) ng/mL) and control group (24.80 (15.50 – 31.50) ng/mL). Serum NGAL was well correlated with Geobes score, Mayo score, CRP and ESR. Serum NGAL at cut-off ≥ 63 can predict activity with sensitivity 88.89%, specificity 85.71%, PPV 94.12% and NPV 75%.

Conclusion: Serum NGAL is valuable noninvasive marker for assessment of UC disease activity.

Keywords: Disease activity; neutrophil gelatinase-associated lipocalin; ulcerative colitis; geobes score; mayo score.

1. INTRODUCTION

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease (IBD) which has a course of relapse and remission. UC seems to have an equal distribution on both sexes. Inflammation starts in the rectum characteristically, spreading proximally continually, confluent and concentrically to impact a variable width of the colon or the whole mucosal surface [1].

It is crucial to determine the activity of the disease and to anticipate treatment effects in UC cases. The assessment is based on clinical, serological and endoscopic tests [2].

The non-invasive inexpensive serologic tests are usually used to assess the degree of inflammation and to track the activity of the disease, because no single method proved to be effective in measuring the activity of the disease [3]. But endoscopy and biopsy are expensive, time consuming and potentially risky. Therefore, it is essential to establish the relationship between histologic findings and other indices to track activity and to predict the treatment outcome of UC cases [4].

NGAL is found in different cell types; neutrophils, adipocytes and epithelium of the gastrointestinal, urogenital and respiratory tracts [5,6]. In many disorders including inflammatory conditions, NGAL was reviewed as a diagnostic and prognostic biomarker due to its small mass (25 kDa) and relative stability [6,7].

The objective of this study was to assess the relationship between NGAL and endoscopic, histopathologic and clinical activity of UC.

2. METHODS

This prospective cohort study was conducted from March 2018 to August 2019, after obtaining an informed written consent and the approval from Tanta University Ethical Committee (code number: 32132/02/18). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).Fifty adult cases with definitive diagnosis of UC (confirmed by clinical, endoscopic, and histological workup) were recruited prospectively among individuals undergoing colonoscopy selected from out-patient's clinic and in-patient's wards of Gastroenterology and Hepatology Unit of Internal Medicine Department at Tanta University Hospitals. Healthy controls were 15 cases who had normal colonoscopy. UC cases were recruited at any time during the treatment and divided into active and inactive according to histopathological activity (Geobes score). Patients were considered active if Geobes score was ≥3.1.

Exclusion criteria were patients with malignancies, hepatic insufficiency, renal dysfunction, diabetes mellitus or cardiovascular diseases and patients on topical treatment for UC.

2.1 All Cases Were Subjected to the Following

Thorough history taking, complete clinical examination, Laboratory investigations including Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels and liver and kidney function tests.

Serum NGAL estimation using ELISA technique (Use a serum separator tube and allow 5-10 min to be clotted until centrifugation at room temperature for 5 min at 4000 r.p.m. serum was separated and stored at -20°C. Centrifuging the specimen again before thawing. Avoid repeated freeze thaw cycles).

Colonoscopy with biopsy: Endoscopy was performed to assess activity of UC and to exclude malignant transformation. High-definition video scope (epk©i.scan 5000) was used in all examinations (Pentax medical. Japan).The endoscopic disease activities were assessed by Mayo endoscopic subscore [8] (0: Inactive disease and normal mucosa, 1: Mild, 2: moderate, 3: Severe disease). Biopsies was obtained from inflamed or healed colonic mucosa or from random sites of sigmoid colon or rectum if inflamed area wasn't found. Histopathological activity was assessed using Geobes scores [9].

2.2 Statistical Analysis

The data collected were analyzed by SPSS version 26 (IBM®, USA). Shapiro-Wilks normality test was used to test the distribution of quantitative variables to select accordingly the type of statistical testing: Parametric or nonparametric. Quantitative parametric data (e.g. age) were presented as range, mean and standard deviation (SD) and were compared by unpaired Student t-test if two groups and by ANOVA test if 3 groups (with post hoc test (LSD) to compare each two groups). Quantitative non-parametric data (e.g. NGAL) were presented as median and interquartile range (IQR) and were analyzed using Kruskal-Wallis test; further analysis was performed by Mann–Whitney (U) test to compare each two groups. Categorical data (e.g. sex) were presented as number and percentage and were compared by chi-square (X^2) test. Correlation between two quantitative data was assessed by Pearson correlation coefficient (r). Assessment of NGAL performance was done by ROC curve analysis. A P value < 0.05 was considered statistically significant.

3. RESULTS

UC cases were classified into group A (active group; n = 36) and group B (inactive group; n = 14).

The mean value (± SD) of age was 34.28 ± 9.00 years in group A, 33.14 ± 9.08 years in group B and 38.87 ± 10.20 years in group C. There were 13 male (36.11%) and 23 female cases (63.89%) in group A, 6 male cases (42.86%) and 8 female cases (57.14%) in group B and 4 male cases (26.67%) and 11 female cases (73.33%) in group C. Symptoms of all patients are shown in Table 1. Medications, Mayo score, colonoscopy and histopathological findings and extensions of ulcerative colitis cases are shown in Table 2.

Hb showed significant decrease in group A than group B and C and group B than C.TLC showed significant increase in group A than B and group C while there was insignificant difference between group B and C. Platelet showed insignificant difference among the three groups. ESR at the first hour showed significant increase in group A than B and group C while there was insignificant difference between group B and C. ESR at the second hour showed significant increase in group A than B and group C and in group B than C.CRP showed significant increase in group A than B and group C while there was insignificant difference between group B and C(Table 3).

The median value (IQR) of NGAL was 101.15 (67.53 – 156.40) ng/mL in group A, 63.35 (60.98 – 65.20) ng/mL in group B and 24.80 (15.50 – 31.50) ng/mL in group C and there was significant increase in group A than B and C and in group B than C (Table 4).

Table 1. Patients' characteristics

		Group A (Active) n = 36	Group B (Inactive) n = 14	Group C (Control) n = 15	P- value
Age (y)	Mean ± SD	34.28 ± 9.00	33.14 ± 9.08	38.87 ± 10.20	0.195
Sex	Male / Female	13 / 23	6 / 8	4 / 11	0.654
Symptoms N (%)	Asymptomatic	0 (0.00%)	9 (64.28%)	0 (0.00%)	<0.001[a]
	Abdominal pain	33 (91.67%)	1 (7.14%)	7 (46.67%)	
	Gaseous distention	32 (88.89%)	4 (28.57%)	4 (26.67%)	
	Diarrhea	34 (94.44%)	3 (21.42%)	6 (40.00%)	
	Fresh bleeding per rectum	28 (77.78%)	0 (0.00%)	0 (0.00%)	
	Fever	14 (38.89%)	0 (0.00%)	0 (0.00%)	

[a] *Significant as P value <0.05*

Table 2. Medications, colonoscopicand histopathological findings, Mayo score and extensions of the disease

		Group A (Active) n = 36	Group B (Inactive) n = 14	P
Medications N (%)	5-ASA	28 (77.78%)	7 (50.00%)	0.319
	Steroids	17 (47.22%)	8 (57.14%)	
	Azathioprine	6 (16.67%)	3 (21.43%)	
	TNF-alpha inhibitor	6 (16.67%)	0 (0.00%)	
Colonoscopic findings N (%)	Erythematous mucosa	36 (100%)	1 (7.14%)	<0.001[a]
	Diffuse ulcerations with contact bleeding	26 (74.3%)	0 (0%)	
	Pseudo-polyps	6 (17.1%)	0 (0%)	
Histo-pathological findings N (%)	Grade 0: architectural changes	36 (100%)	0 (0%)	--------
	Grade 1: Chronic inflammatory infiltrate	36 (100%)	0 (0%)	
	Grade 2: Lamina properia neutrophils and eosinophils	36 (100%)	0 (0%)	
	Grade 3: Neutrophils in epithelium	36 (100%)	0 (0%)	
	Grade 4: Crypt destruction	17 (47.2%)	0 (0%)	
	Grade 5: Erosion or ulceration	12 (33.3%)	0 (0%)	
Mayo score N (%)	0-2 (Remission)	0 (0%)	14 (100%)	<0.001[a]
	3-6 (Mild)	17 (47.22%)	0 (0%)	
	7-9 (Moderate)	11 (30.56%)	0 (0%)	
	>10 (Severe)	8 (22.22%)	0 (0%)	
Extensions of the disease N (%)	Rectum	11 (31.4%)	13 (92.86%)	<0.001[a]
	Left sided	18 (51.4%)	1 (7.14%)	
	Pancolitis	7 (20%)	0 (0.0%)	

[a] *Significant as P value <0.05*

Table 3. Laboratory investigations of the studied patients

		Group A (Active) n = 36	Group B (Inactive) n = 14	Group C (Control) n = 15	P value [a]	Post Hoc (LSD)	
Hb (gm/dL)	M ± SD	10.89 ± 1.43	12.16 ± 1.65	13.53 ± 0.82	< 0.001[a]	P1	0.005[a]
						P2	<0.001[a]
						P3	0.009[a]
Platelet ($^b10^3/mm^3$)		312.42 ± 92.11	274.79 ± 86.57	284.64 ± 72.66	0.31		
TLC ($^b10^3/mm^3$)		12.97 ± 2.99	6.54 ± 2.11	6.57 ± 1.66	< 0.001[a]	P1	<0.001[a]
						P2	<0.001[a]
						P3	0.976
ESR 1st hour (mm/h)		42.22 ± 19.55	16.07 ± 9.46	5.40 ± 2.53	<0.001[a]	P1	<0.001[a]
						P2	<0.001[a]
						P3	0.067
ESR 2nd hour(mm/h)		74.72 ± 30.02	32.50 ± 20.82	13.33 ± 3.46	<0.001[a]	P1	<0.001[a]
						P2	<0.001[a]
						P3	0.04[a]
CRP (mg/dL)		34.28 ± 30.52	16.71 ± 17.16	1.80 ± 1.66	<0.001[a]	P1	0.025[a]
						P2	<0.001[a]
						P3	0.103

Hb: Hemoglobin, TLC: Total leucocytic count, ESR: Erythrocyte Sedimentation Rate, CRP: C reactive protein P1: Comparison between group A and B, P2: Comparison between group A and C, P3: Comparison between group B and C.[a] significant as P value <0.05

Table 4. NGAL of the studied patients

	Group A (Active) n = 36	Group B (Inactive) n = 14	Group C (Control) n = 15	P value		
NGAL (Median (IQR))	101.15 (67.53 – 156.40)	63.35(60.98 – 65.20)	24.80 (15.50 – 31.50)	< **0.001** [a]	P1	**<0.001** [a]
					P2	**<0.001** [a]
					P3	**<0.001** [a]

NGAL: Neutrophil gelatinase-associated lipocalin, IQR: Interquartile range, P1: Comparison between group A and B, P2: Comparison between group A and C, P3: Comparison between group B and C.[a] significant as P value <0.05

Table 5. ROC curve of NGAL to predict activity

Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
≥ 63	88.89 (73.9-96.9)	85.71 (57.2-98.2)	94.12 (81.52-98.31)	75 (53.75-88.57)	0.941 (0.837 - 0.988)

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve

At cut-off ≥ 63 of NGAL to predict activity, sensitivity was 88.89%, specificity was 85.71%, PPV was 94.12% and NPV was 75%. AUC was 0.941, Youden index was 0.806 and P value was <0.001(Table 5 and Fig. 1).

There was strong positive significant correlation between NGAL and Geobes score (r = 0.882, P <0.001), Mayo score (r = 0.75, P <0.001) and CRP (r = 0.779, P<0.001). There was moderate positive significant correlation between ESR and NGAL (r = 0.596, P <0.001) (Fig. 2).

4. DISCUSSION

Despite the benefits of recognizing the UC, in the recent years very little was accomplished in the context of evaluation and tracking of UC. An increasing need has been developed for further diagnostic and monitoring biomarkers [10].

Nowadays, the "gold standard" techniques for the diagnosis and monitoring of the UC depend on clinical assessment, fecal or serological biomarkers and endoscopy. Colonoscopy, though, is an expensive technique associated with patient discomfort and had many risks such as perforation [11]. In the contrast to this, both fecal and serological biomarkers are easily used, easily reproducible, objective and less invasive methods [12]. NGAL has been used as a diagnostic marker for many diseases (e.g. AKI, CKD, IBD) and as a prognostic marker (e.g. sepsis, DM) [6]. Some studies found that there is an over expression of NGAL in the colon epithelium, suggesting that NGAL evaluation may help in studying the pathophysiology of IBD and assessment of the disease activity [13].

In our study, TLC showed significant increase in group A than B and group C. In the same line of our results, Yesil et al. [14] revealed that TLC was significantly higher in UC group than controls. ESR at the 1st hour and CRP showed significant increase in group A than B and group C. ESR at the 2nd hour showed significant increase in group A than B and group C and in group B than C). Similarly to our results, Nooh et al. [15] documented that there was a highly significant increase in ESR (first hour) and CRP of active UC when compared with inactive UC and control groups. Also, Yesil et al. [14], revealed that WBC, ESR and CRP were significantly higher in UC group than healthy control group.

In our study, the median value (IQR) of NGAL was 101.15 (67.53 – 156.40) ng/mL in group A, 63.35 (60.98 – 65.20) ng/mL in group B and 24.80 (15.50 – 31.50) ng/mL in group C and there was significant increase in group A than B and C and in group B than C. Similarly to our results, Nooh et al. [15] showed that there was a highly significant elevation of serum NGAL in active UC (90.62 ± 67.87 ng/ml) when compared with inactive UC (25.68 ± 6.10 ng/ml) and the control group (9.12 ± 3.30 ng/ml). Moreover, Budzynska et al. [16] revealed that NGAL concentrations were significantly lower in cases with complete endoscopic and histologic remission than in the active UC (46.9 versus 66.4 ng/ml, P = 0.009). Stallhofer et al. [17] found that serum NGAL was significantly increased in in active UC than controls (median 42.21 [28.97–73.74] vs 24.22 [17.76–35.25] ng/mL). Also, Yesil et al. [14] revealed that serum NGAL was higher in the UC group compared to controls [median 188, IQR (142–264) vs 107 (45-234) ng/mL]. Oikonomou et al. [18] showed that serum NGAL was increased in UC compared with controls (86.62 ± 35.40 vs 60.06 ± 24.18 ng/mL)and in active UC compared to inactive UC (120.10 ± 33.65 vs 64.32 ± 14.77 ng/mL). Unlike to our results, Yesil et al. [14] revealed that serum NGAL concentrations did not differ between in quiescent versus active stages.

Our study revealed that at cut-off ≥ 63 of NGAL to predict activity, sensitivity was 88.89%, specificity was 85.71%, PPV was 94.12% and NPV was 75%. AUC was 0.941 and P value was <0.001. Nooh et al. [15] showed that serum NGAL at cut-off point 33.7 ng/ml could detect disease activity in UC cases [sensitivity (100%), specificity (84%), accuracy (92.0%), PPV (86.2%), NPV (100%)].

Budzynska et al. [16] showed the optimal serum NGAL cut-off to discriminate active and inactive form was 43.6 ng/ml with AUC 0.79, sensitivity of 96% and a specificity of 50%. Stallhofer et al. 2015 [17] showed that serum NGAL at cutoff level of 27.75 ng/mL displayed a sensitivity of 0.83 and a specificity of 0.64 to distinguish active UC from UC in remission and AUC 0.75. Yesil et al. [14] revealed that a cut-off level of serum NGAL of 129 ng/mL was used to distinguish IBD from healthy control, a sensitivity of 76.1% and a specificity of 60.9% was reached. Also, Oikonomou et al. [18] found that in differentiating IBS from active UC, a sensitivity of 97% and a specificity of 81% at cutoff of 96 ng/mL which was better than ESR and CRP.

Serum NGAL is correlated positively with inflammatory markers (CRP and ESR) and

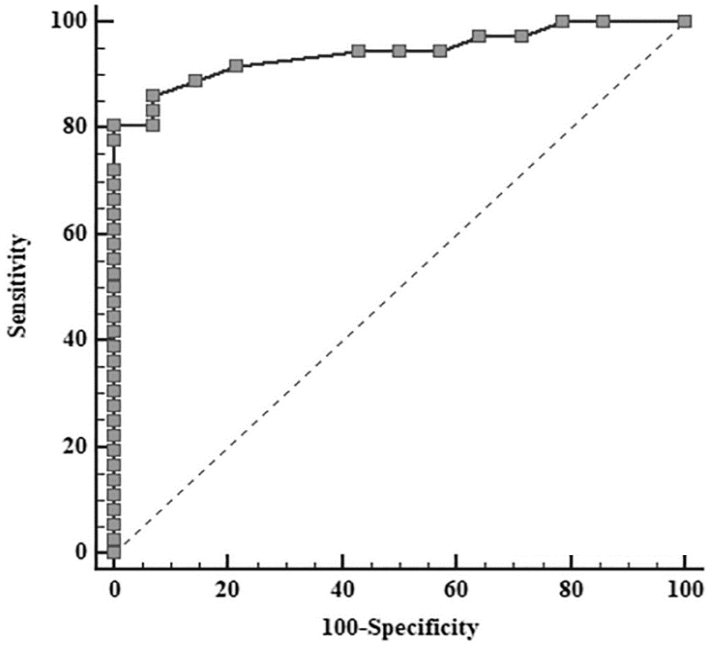

Fig. 1. ROC curve of NGAL to predict activity

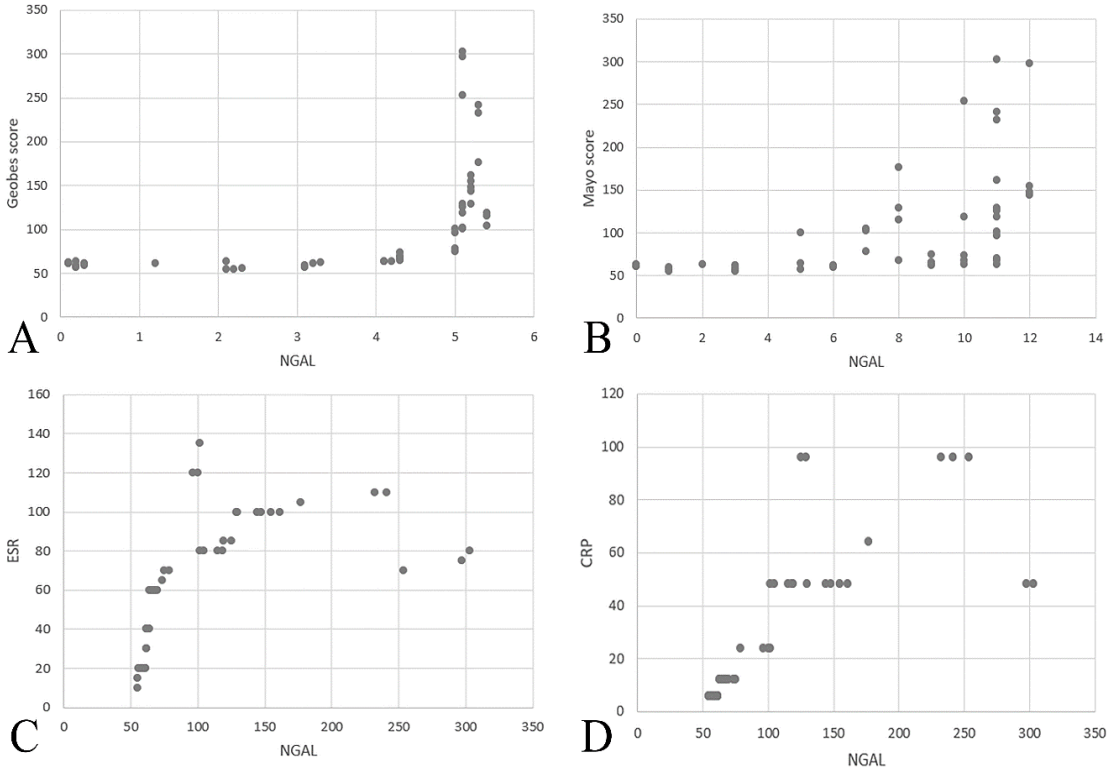

Fig. 2. Correlation between NGAL and (A) Geobes score, (B) Mayo score, (C) ESR, (D) CRP

markers of disease activity (Mayo and UC histopathology grading). Similarly to our results, Nooh et al. [15] found that in UC cases, serum NGAL was correlated highly significantly with

ESR, CRP, UCAI and Geobes score. Also, Budzynska et al. [16] showed that NGAL levels correlated with CRP, ESR and Mayo score. Moreover, Stallhofer et al. [17] showed that serum LCN2 is moderately correlated with CRP in UC cases. Oikonomou et al. [18] found that serum NGAL is correlated with CRP, ESR and Mayo score in UC cases. Unlike to our results, Yesil et al. [14] revealed that no significant correlation was found between endoscopic Mayo scores and NGAL levels.

The discrepancy in the cut-off value of NGAL between different studies may be due to different populations and different number of cases and controls.

The limitations of the study were small sample size and being single center study. Further studies on large number of patients with lower GIT symptoms to determine any role of serum NGAL in organic colonic diseases other than UC including CRC in non-UC patients. Also, further studies to evaluate the role of NGAL in assessing response to therapy for UC.

5. CONCLUSION

In conclusion, serum NGAL is a valuable non-invasive marker in assessment of UC activity and correlated positively with inflammatory markers (CRP and ESR) and markers of disease activity (Mayo and UC histopathology grading). Serum NGAL at cut off point ≥ 63 to predict activity, sensitivity was 88.89%, specificity was 85.71%, PPV was 94.12% and NPV was 75%.

CONSENT AND ETHICAL APPROVAL

This prospective cohort study was conducted from March 2018 to August 2019, after obtaining an informed written consent and the approval from Tanta University Ethical Committee (code number: 32132/02/18). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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