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Can the neutrophil–lymphocyte ratio, platelet–lymphocyte ratio and lymphocyte–monocyte ratio predict active bleeding in patients with upper gastrointestinal bleeding?

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ABSTRACT

Objective: To investigate the relationship between upper gastrointestinal bleeding and neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR), and examine whether they can be used as markers of inflammation.

Methods: The retrospective single-center study included a total of 189 patients with upper gastrointestinal bleeding admitted to the tertiary emergency department between January 2018 and January 2019. Besides, 59 patients with similar demographic characteristics were selected as the control group. Besides, 42 patients with active bleeding and 147 patients without active bleeding were categorized into two groups according to their endoscopy reports. The NLR, PLR, LMR values, potential risk factors, and demographic characteristics were analyzed.

Results: The mean NLR levels were found significantly higher in the patient group compared to the control group (P<0.001), whereas the mean LMR levels were significantly lower in the patient group (P<0.001). The mean NLR and PLR levels were significantly higher in patients with active bleeding compared to those without active bleeding (P<0.001), whereas the mean LMR levels were significantly lower (P<0.001) for patients with active bleeding. The optimal cut-off value of NLR was found 2.1 for predicting uppergastrointestinal bleeding, with a sensitivity of 80.2% and specificity of 78.9% (AUC: 0.840; P <0.001).

Conclusions: NLR was determined to be a parameter that can be used as an indicator of active bleeding in patients with upper gastrointestinal bleeding.

KEYWORDS: Neutrophil lymphocyte ratio; Platelet lymphocyte ratio; Upper gastrointestinal bleeding; Emergency department

1. Introduction

Upper GI bleeding (UGIB), is one of the most common causes for emergency department (ED) admissions, with an incidence of 50-150 patients per 100 000 people, and is associated with high mortality and morbidity[1]. Despite improvements in the diagnosis and treatment methods, the mortality rate of UGIB remains around 10%. Therefore, early diagnosis of UGIB is of great importance for the determination of the severity of bleeding and initiation of early treatment. Considering that, routine use of low-cost and applicable parameters may be highly useful for the diagnosis and treatment of patients with UGIB[2,3].

Previous studies have demonstrated a relationship between elevated platelet, leukocyte, and C-reactive protein (CRP) levels and UGIB[4,5]. It has also been reported that a decrease in mean platelet volume (MPV) may be an indicator of the severity and prognosis of UGIB[6]. Recent studies have demonstrated that low-cost and easily obtainable parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte monocyte ratio (LMR) can be used as markers of inflammation in many diseases[7-9]. Also, the NLR, PLR, LMR levels have been shown to increase in many diseases such as cardiovascular diseases, peripheral artery diseases, cerebrovascular events, and malignancies[10]. A few

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studies have evaluated the relationship between the inflammatory markers including NLR, PLR, LMR, and UGIB patients. Therefore, our study aims to investigate the relationship between NLR, PLR, LMR, and UGIB.

2. Materials and methods

2.1. Ethical approval

This retrospective study was conducted in the emergency department of Health Science University Antalya Training and Research Hospital, Antalya, Turkey, upon the approval of the Ethics Committee of Antalya Training and Research Hospital under no.2019/315 by the Helsinki Declaration Principles.

2.2. Participants

The study included a total of 189 patients above 18 years of age, who were admitted to the ED diagnosed with UGIP after undergoing upper gastrointestinal system endoscopy between January 1st 2018 to January 1st 2019. UGIB is diagnosed in patients presenting with at least one of the symptoms such as melena, hematochezia, hematemesis (vomiting of coffee-ground-like material), bloody nasogastric aspirate, and detection of bleeding at endoscopy. Patients who were under the age of 18, patients presenting with hemorrhage secondary to trauma, patients with missing data, patients with end-stage renal and hepatic diseases, and those with any known hematologic and ontological malignancies were excluded from the study. We also recruited 59 healthy patients with matched age and gender as the control group. The control group was made up of individuals with no known inflammatory diseases and chronic drug use.

2.3. Data collection

Age, gender, vital signs, hemogram, biochemical parameters, endoscopic findings, duration of hospital stay, and 30-day mortality of the patients and healthy controls were obtained from the hospital registration system. A complete blood count was performed within 1 h as a routine hospital procedure.

2.4. Statistical analysis

The statistical analysis of all variables was carried out using SPSS 18.0. Continuous variables were expressed as mean±standard deviation. Frequency and percentage (%) were used to define categorical data. Pearson's *Chi*-square and Fischer's exact test were used for evaluating the categorical variables. Student *t*-test or Mann Whitney *U* test was used to compare the parameters of the patient group and the control group for normally distributed variables. The significance level of this study was set at α=0.05.

3. Results

The mean age of the patients was (61.73±18.60) years, and the mean age of the healthy controls was (55.51±19.98) years. Concerning gender, 135 patients (71.4%) were male and 54 patients (28.6%) were female. Of the control group, 35 (61.4%) were male, and 22 (38.6%) were female. There was no statistically significant difference in age and gender between the patient group and the control group (P>0.05). The mean white blood cell (WBC), and NLR levels of the patient group were significantly higher compared with the control group, while the mean LMR, hemoglobin (Hb), and haematocrit levels were significantly lower in the patient group (P<0.001 for all parameters). The demographic data and lab results are shown in Table 1.

Active UGIB was detected in 22.2% of patients in the patient group. The mean age of patients presenting with active bleeding was significantly higher than those without active bleeding [(65.77±18.59) years *v.s.* (60.75±18.41) years, P=0.04). Patients with active bleeding tended to present with significantly lower systolic blood pressure [(97.08±12.31) mmHg *v.s.* (119.08±20.93) mmHg, P<0.001] and significantly higher heart rate (beats per minute) (111.26±21.07 *v.s.* 97.74±19.54, P<0.001) at admission. In patients with active bleeding, the mean NLR and PLR levels were found significantly higher than those without active bleeding, whereas the mean LMR and Hb levels were significantly lower (Table 2).

The multivariate logistic regression analysis demonstrated that increased age (adjusted *OR*: 0.380, 95%*CI*: 0.170-0.852, P=0.016), SBP (adjusted *OR*: 2.138, 95%*CI*: 1.400-3.265, P<0.001), HR (adjusted *OR*: 0.305, 95%*CI*: 0.143-0.650, P=0.002), NLR

Table 1. Comparison between the upper gastrointestinal bleeding group and the control groupe regarding the study parameter.

Parameter	Patient group (n=189)	Control group (n=57)	$t/\chi^2/U$	P-value
Age (years)	61.73±18.60	55.51±19.98	2.14	0.320
Gender (male/female) [n (%)]	135/54 (71.4%/28.6%)	35/22 (61.4%/38.6%)	1.43	0.190
WBC count ($\times10^3$/mm^3)	10.92 (4.92-16.92)	8.60 (5.99-11.47)	–5.71	<0.001
NLR	5.51 (2.52-7.78)	3.84 (2.18-7.95)	–7.74	<0.001
PLR	122.85 (94.83-234.84)	112.73 (67.45-240.52)	–2.01	0.761
LMR	3.26 (1.89-4.64)	3.57 (0.84-10.62)	–4.41	<0.001
Hb (g/dL)	9.80±3.61	13.31±1.24	2.69	<0.001
Hct (%)	30.03±9.10	40.12±3.42	1.76	<0.001
MPV (fL)	8.73 (8.52-8.93)	8.71 (8.40-9.08)	0.21	0.863

UGIB: upper gastrointestinal bleeding; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; LMR: lymphocyte monocyte ratio; Hb: hemoglobin; Hct: hematocrit; MPV: mean platelet volume. WBC count, NLR, PLR, LMR, MPV are expressed as median (IQR).

Table 2. Comparison of characteristics, laboratory parameters, and outcomes between patients with and without active bleeding.

Parameter	Active blooding (n=42)	No active bleeding (n=147)	$t/\chi^2/U$	P-value
Age (years)	65.77±18.59	60.75±18.41	0.62	0.040
Gender (male/female) [n (%)]	29/13 (69%/31%)	105/41 (71.9%/28.1%)	–2.12	0.703
Number of co-morbid conditions	1.00 (0.62-2.14)	0.75 (0.5-1.25)	0.72	0.586
SBP (mmHg)	97.08±12.31	119.08±20.93	–0.58	<0.001
Heart rate (beats per minute)	111.26±21.07	97.74±19.54	–0.36	<0.001
WBC count ($\times10^3$/mm^3)	9.77±4.83	9.09±3.92	–0.65	0.350
NLR	10.50 (4.50-16.35)	3.50 (2.56-7.18)	–1.21	<0.001
PLR	186.47 (148.71-223.22)	132.91 (98)	–1.67	<0.001
LMR	2.60 (2.20-7.01)	2.66 (2.79-3.87)	–0.31	0.005
Hb (g/dL)	9.26±2.95	10.53±3.65	2.22	0.039
Hct (%)	29.83±12.15	31.45±7.58	1.63	0.117
MPV (fL)	8.52±1.25	8.77±1.19	–0.66	0.097
BUN (mg/dL)	35.42 (26.68-44.16)	33.95 (29.93-37.93)	–3.31	0.461
Creatinine (mg/dL)	1.36 (0.89-1.82)	1.00 (1.09-1.52)	–0.75	0.448
BUN/Cr	28.85±13.08	29.76±13.78	1.25	0.764
Length of hospital stay (day)	4.00 (3.37-8.68)	5.08 (4.31-5.85)	–0.44	0.169
30-day mortality [n (%)]	3 (8.1%)	2 (1.3%)	–1.54	0.029

SBP: systolic blood pressure; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; LMR: lymphocyte monocyte ratio; Hb: hemoglobin; Hct: hematocrit; MPV: mean platelet volume; BUN: blood urea nitrogen; BUN/Cr: blood urea nitrogen to creatinine ratio. Number of co-morbid conditions, NLR, PLR, LMR, BUN, creatinine, and length of hospital stay are expressed as median (IQR).

Table 3. Logistic regression analysis for possible risk factors of active upper gastrointestinal bleeding.

Variables	*OR*	95%*CI*	P-value
Age (≥65 *v.s.* <65)	2.646	1.356-4.768	0.030
Sex (male *v.s.* female)	1.148	0.544-2.423	0.717
SBP (≥120 *v.s.* <120)	2.138	1.400-3.265	<0.001
HR (≥100 *v.s.* <100)	0.305	0.143-0.650	0.002
NLR (≥4.3 *v.s.* <4.3)	0.207	0.092-0.469	<0.001
PLR (≥135.4 *v.s.* <135.4)	0.276	0.122-0.622	0.001
LMR(≥3.55 *v.s.* <3.55)	1.954	0.918-4.160	0.079
Hb(≥9.8 *v.s.* <9.8)	1.505	0.638-3.552	0.349

SBP: systolic blood pressure; NLR: neutrophil-lymphocyte ratio; PLR: platelet lymphocyte ratio; LMR: lymphocyte monocyte ratio; Hb: hemoglobin.

Table 4. Etiologies of acute upper gastrointestinal bleeding.

Parameters	Active bleeding (n=42) [n (%)]	No active bleeding (n=147) [n (%)]	χ^2	P-value
Peptic ulcer	19 (45.2%)	82 (55.7%)	–6.104	<0.001
Esophagogastric varix	12 (28.6%)	18 (12.2%)	–3.507	<0.001
Mallory-Weiss syndrome	1 (2.4%)	8 (5.5%)	0.478	0.039
Neoplasm	6 (14.3%)	9 (6.1%)	–4.102	0.172
Esophagitis	4 (9.5%)	9 (6.1%)	–2.705	0.278
Angiodysplasia	0 (0)	4 (2.8%)	1.970	0.084
Unspecified	0 (0)	17 (11.6%)	2.172	<0.001

(adjusted *OR*: 0.207, 95%*CI*: 0.092-0.469, P <0.001) and PLR (adjusted *OR*: 0.276, 95%*CI*: 0.122-0.622, P<0.001) were associated with increased risk of active bleeding in patients with UGIB (Table 3). Besides, it was shown that the NLR cut-off value of 2.1 can be used for predicting UGIB with an AUC of 0.840, the sensitivity of 80.2%, and specificity of 78.9%; whereas the NLR cut-off value of 4.3 can be used for predicting active bleeding in UGIB patients with an AUC of 0.840, sensitivity of 69.2% and specificity of 70.4%.

The possible etiologies of UGIB in patients are described in Table 4. There was a significant difference in the distribution of etiologies between patients with and without active bleeding (χ^2=–1.380, P=0.011). In addition, esophagogastric varix and neoplasm were more common in patients with active bleeding.

4. Discussion

UGIB is a condition associated with high mortality and morbidity despite technological advances in diagnosis and treatment methods[11]. However, early prediction of active bleeding in the patients will avoid unnecessary procedures and interventions, and possibly increase the survival rate[12]. This study demonstrates that elevated NLR is associated with a high risk of active bleeding

in patients with UGIB. Thus, NLR may be clinically useful as a predictor of active bleeding in patients with UGIB.

Previous studies have demonstrated the association between UGIB and some parameters including thrombocytosis, leukocytosis, elevated CRP, total bilirubin, blood urea nitrogen, PLR values[4,11]. Also, recent studies have reported that MPV levels are significantly lower in patients with UGIB than in healthy controls[5,13]. Our study results have demonstrated that lower LMR, Hb, and Hct levels, as well as elevated WBC and NLR levels, were associated with UGIB. Similar to other studies, elevated NLR and PLR levels were found to be associated with UGIB in our study.

Several studies have demonstrated the association between elevated NLR, PLR, CRP, and many inflammatory diseases such as ulcerative colitis and Crohn's disease[14,15]. A study carried out by Makay *et al.* including 63 Henoch-Schönlein purpura patients reported that elevated NLR and decreased MPV values were risk factors for gastrointestinal bleeding[16]. Park *et al.* reported that the NLR cut-off value of 3.18 could predict easy recovery in gastrointestinal bleeding and the NLR cut-off value of 3.90 could predict GI bleeding[17]. The study conducted by Gayret *et al.* demonstrated that NLR and PLR were increased in patients with Henoch-Schönlein purpura, but only reported PLR as an indicator of gastrointestinal bleeding in these patients[4]. In our study, the optimal cut-off value of NLR was found 2.1 for predicting UGIB, with an AUC of 0.840, sensitivity of 80.2%, and specificity of 78.9%.

Previous studies have indicated that lactate clearance, Hb, total bilirubin International normalized ratio (INR), and PLR may be a marker of active bleeding in patients with UGIB[11]. Makay *et al.* reported that WBC, CRP, and platelet levels were higher among the UGIB patients with active bleeding compared to those without active bleeding (P=0.004, P=0.03, and P=0.03, respectively)[13]. Another study by Gayret *et al.* found a positive relationship between elevated PLR and platelets and active bleeding. However, there was no statistical significance although NLR was found to be higher in patients with active bleeding[4]. In our study, the mean NLR and PLR levels were found significantly higher, and the mean LMR and Hb levels were significantly lower in patients with active bleeding compared to those without active bleeding.

The most common endoscopic finding in patients with UGIB is peptic ulcer[18]. A study reported that the most common etiologies of UGIB were peptic ulcer (63.2%) and esophageal varices (9.4%)[19]. Another study targeted at patients with UGIB also reported the most common etiologies as peptic ulcer and esophageal varices in patients whether presented with active bleeding or not[11]. Consistent with the literature, the most common etiologies were also peptic ulcer and esophageal varus in our study. In addition, esophagogastric varix and neoplasm were more common in patients with active bleeding. Physicians may be more careful in patients with active bleeding risk such as these diseases.

Our study had some limitations. Firstly, our study was designed retrospectively and included a relatively small number of patients. Secondly, physical examination findings, symptoms, and the period between the onset of UGIB and admission to the emergency department could not be determined clearly. Another limitation was that the treatment and protocols applied to patients might vary from location. We recommend that multicenter and prospective studies should be carried out.

To conclude, NLR is an independent risk factor for active bleeding in patients with UGIB. This parameter can be measured easily, quickly, and without additional cost to the patient. NLR can be considered as a parameter in the development of risk scoring systems.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

C.B. and M.K.: study design, data collection, data analysis, and manuscript preparation, and final edition. C.B., M.K., F.S., Y.K. had role in manuscript preparation and data analysis.

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