Original Research Article

Diagnostic Value of Inflammatory Factors in Patients with Gallbladder Cancer, Dysplasia, and Cholecystitis

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Abstract

Background: Involving pre-sampled patients with cholecystitis, dysplasia, and adenocarcinoma, the present study aimed to compare the neutrophil/lymphocyte (NLR), monocyte/lymphocyte (MLR), platelet/lymphocyte (PLR) ratios, and plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) values and to determine their prognostic importance.

Methods: The present study involved 187 cholecystectomy specimens that were diagnosed as cholecystitis, dysplasia, and adenocarcinoma. Preoperative neutrophil, monocyte, lymphocyte, and platelet counts, NLR, MLR, and PLR ratios, and PCT, MPV, and PDW levels of the same patient groups were retrospectively recorded.

Results: In the present study, the cut-off values for dysplasia of NLR, PLR, and MLR were found as 1.61, 81.45, and .19, whereas those for cancer of NLR, PLR, and MLR were 2.65, 182.69, and .35, respectively. The NLR, PLR, and MLR values of the chronic cholecystitis and chronic calculous cholecystitis groups were statistically significantly lower than those of the chronic active calculous cholecystitis group ($P < .01$). The NLR and MLR values of the non-cancer and non-dysplasia groups were statistically lower than those of the cancer and dysplasia groups ($P < .05$).

Conclusion: According to the results of the present study, using additional imaging methods, acute-phase cholecystitis can be distinguished using preoperative neutrophil and monocyte counts, and NLR, PLR, and MLR cut-off values can be used to distinguish dysplasia, which is the antecedent of gallbladder cancer. It is thought that this might provide patients with an advantage in terms of early treatment and survival.

Keywords

gallbladder pathologies, neutrophil/lymphocyte, platelet/lymphocyte, monocyte/lymphocyte, hemogram parameters, inflammatory response

Introduction

Gallbladder pathologies constitute one of the most frequently seen disease groups in daily practice. In the United States of America, cholelithiasis and chronic cholecystitis affect approximately 10% of the population. Gallbladder pathologies are seen in the fifth-sixth decades.[1,2] Gallbladder cancer (GBC) is relatively rarely seen and causes increased morbidity and mortality throughout the world.[3-7] The rate is approximately 2.5/100000. Most gallbladder tumors are asymptomatic and they are incidentally detected during postoperative histopathologic examinations (approximately .19–3.3%).[3,5] Although its pathogenesis has not been completely revealed, GBC development is generally related to the dysplasia-carcinoma

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chain and, to a lesser extent, the adenoma-carcinoma chain.[1] Despite the advancements in technology in the diagnosis and treatment of GBC, it still has a poor prognosis. This is believed to be because patients are diagnosed late and are at an advanced level by the time of diagnosis.[3,5] Inflammation and immunity are well-known mediator factors in carcinogenesis and tumor progression.[4,5,8–11] Certain cytokines including myeloid growth factors, tumor necrosis factor-α, interleukin (IL)-10, and transforming growth factor-β lead to neutrophilia and relative lymphocytopenia, causing an increase in the neutrophil to lymphocyte ratio (NLR).[4,5,8,11] In fact, tumor-infiltrating lymphocytes are related to better survival and prognosis in various cancers. However, a low lymphocyte count is related to poor prognosis because it may represent an insufficient immune response in certain cancers.[3] In addition, high platelet (PLT) levels and lymphocyte counts were found to be related to poor prognosis in many solid organs. The platelet to lymphocyte ratio (PLR) and NLR, which are also combinations of PLT and lymphocyte counts, are also accepted as representative inflammation indices.[3,12] Besides that, previous studies also focused on indicators such as mean platelet volume (MPV), which indicates the volume of PLTs, as well as the activation and function of PLTs. Mean platelet volume is used to represent the inflammatory load and disease activity in various diseases. Plateletcrit (PCT) and platelet distribution width (PDW) are 2 complete blood count parameters related to platelets.[13] Platelets, and consequently relevant parameters such as PCT, PLT, and PDW change in response to stimulants in systematic inflammatory processes and various tumors.[13,14] In some previous studies, it was reported that pancreatic and ovarian cancers were well-known thrombogenic cancers, and also thrombocytosis was observed besides high tissue factor and vascular endothelial growth factor (VEGF) expression. Serum VEGF levels and platelet counts were reported to have a significant correlation.[8,15] Platelets are activated by pro-inflammatory cytokines such as IL-1 and IL-6, angiogenic growth factors are released, and tumor prognosis-metastasis is promoted.[8,16] In other words, thrombocytosis is an indicator of the severity of inflammation. Platelet to lymphocyte ratio was reported to be a predictor of poor survival.[14] Few studies have examined the prognostic importance of PLR, NLR, monocyte/lymphocyte (MLR), PCT, MPV, and PDW in GBC, which is one of the malignancies strongly related to chronic inflammation, and gallbladder pathologies. For this reason, the present study was conducted as a cohort study aiming to reveal the prognostic value of PLR, NLR, MLR, PCT, MPV, and PDW in GBC and gallbladder pathologies.

Materials and Methods

Study Design and Data Sources

The biochemical data used in the present study were obtained from the hospital data processing system (HBİS). Among the whole blood parameters, neutrophil 2-7 ($\times 10^3/\mu L$), lymphocyte .8-4 ($\times 10^3/\mu L$), monocyte .12-1.2 ($\times 10^3/\mu L$), and PLT 150-450 ($\times 10^3/\mu L$) counts and platelet indices [platelet volume (MPV) 6.5-12 (Fl), PCT .1-.28 (%), and PDW 10-65 (%)] were analyzed using a BC 6800 (Mindray, China) automatic hematology analyzer. Neutrophil, monocyte, and PLT counts were divided by lymphocyte counts and NLR, MLR, and PLR were calculated. The data obtained from HBİS and the calculated ratios were entered into the SPSS 21 program. Within the scope of the present study, the slides of 187 cholecystectomy specimens, which were sampled between 2016 and 2020 in the Department of Pathology in Uşak University's Training and Research Hospital and diagnosed as cholecystitis, dysplasia, and adenocarcinoma, were re-examined. Adenocarcinoma, dysplasia, metaplasia, cholelithiasis, cholesterolosis, and other lesions were re-investigated using an Olympus CX41 light microscope and the final diagnoses were considered. Pathologic staging of tumors was performed in accordance with the criteria of the American Joint Committee on Cancer (AJCC). In Uşak Training and Research Hospital's Biochemistry Department, the same patient groups' preoperative NLR, MLR, and PLR values were retrospectively recorded. Comparing these data, their diagnostic values were investigated in these patient groups.

Statistical Analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program. Besides the descriptive statistics (mean, standard deviation, median, frequency, ratio, minimum, and maximum) used in analyzing the study data, the data distribution was tested using the Shapiro–Wilk test. For non-normally distributed quantitative data, the Kruskal–Wallis test was used for comparing three or more groups, and the Mann–Whitney U test was used for comparing 2 groups. The relationship between qualitative data was determined using the Chi-square test, and cut-off values were determined using receiver operating characteristics (ROC) analysis. Statistical significance was set at <.01 and $P < .05$.

Results

It was determined that 22.9% (n = 43) of the participants had chronic cholecystitis, 35.6% (n = 67) had chronic calculous cholecystitis, 3.2% (n = 6) had chronic active calculous cholecystitis, 2.1% (n = 4) had chronic active cholecystitis, and 36.2% (n = 67) were in the others group (dysplasia n = 51, adenocarcinoma n = 9, and xanthogranulomatous and eosinophilic cholecystitis n = 7) (Table 1). Metaplasia was detected in 62.8% (n = 118) of participants, 72.9% (n = 137) had dysplasia, and cholesterolosis was observed in 89.4% (n = 168). Finally, stones were found in 61.2% (n = 115) of the participants.

Neutrophil

The mean neutrophil value was 5.17 ± 2.65 (range, 1.54-19.13). There was a statistically significant difference between

Table 1. Comparison of Parameters by Diagnosis.

		N	Mean ± SD	Min-Max (Median)	*P*
Neutrophil	Chronic cholecystitis	43	4.25 ± 1.21	1.54-6.8 (4.12)	.012*
	Chronic calculous cholecystitis	67	4.94 ± 2.78	2.12-19.13 (4.31)	
	Chronic active calculous Cholecystitis	6	8.18 ± 4.39	4.06-13.71 (6.58)	
	Chronic active cholecystitis	4	6.93 ± 3.39	2.91-11.13 (6.83)	
	Other	67	5.63 ± 2.69	1.86-13.3 (5.02)	
Lymphocyte	Chronic cholecystitis	43	2.44 ± .95	1.18-6.37 (2.33)	**.026***
	Chronic calculous cholecystitis	67	2.38 ± .65	1.12-3.94 (2.34)	
	Chronic active calculous cholecystitis	6	1.92 ± .83	.87-3.19 (1.84)	
	Chronic active cholecystitis	4	2.18 ± .52	1.73-2.89 (2.05)	
	Other	67	1.99 ± .85	.31-4.2 (2)	
Monocyte	Chronic cholecystitis	43	.42 ± .13	.21-.79 (.4)	**.002****
	Chronic calculous cholecystitis	67	.46 ± .18	.21-1.23 (.44)	
	Chronic active calculous cholecystitis	6	.84 ± .43	.5-1.47 (.59)	
	Chronic active cholecystitis	4	.5 ± .2	.2-.64 (.58)	
	Other	67	.5 ± .16	.24-1.01 (.49)	
Platelet	Chronic cholecystitis	43	263.42 ± 73.11	123-500 (252)	.359
	Chronic calculous cholecystitis	67	279.24 ± 72.4	149-525 (274)	
	Chronic active calculous cholecystitis	6	360 ± 193.21	183-720 (309)	
	Chronic active cholecystitis	4	326.75 ± 82.39	230-418 (329.5)	
	Other	67	276.03 ± 78.45	113-471 (271)	
PCT	Chronic cholecystitis	43	.25 ± .07	.14-.44 (.25)	.063
	Chronic calculous cholecystitis	67	.28 ± .09	.14-.67 (.27)	
	Chronic active calculous cholecystitis	6	.34 ± .15	.21-.61 (.3)	
	Chronic active cholecystitis	4	.29 ± .05	.24-.34 (.3)	
	Other	67	.25 ± .07	.1-.45 (.24)	
MPV	Chronic cholecystitis	43	9.62 ± .91	8.2-11.6 (9.5)	**.001****
	Chronic calculous cholecystitis	67	9.8 ± 1.02	7.5-12.1 (9.8)	
	Chronic active calculous cholecystitis	6	9.83 ± .98	8.5-11.2 (9.65)	
	Chronic active cholecystitis	4	9.25 ± 1.1	8.2-10.8 (9)	
	Other	67	9.11 ± 1.17	7.4-13.2 (8.97)	
PDW	Chronic cholecystitis	43	16.06 ± .32	15.3-16.8 (16)	.785
	Chronic calculous cholecystitis	67	16.3 ± 1.53	15.3-25.9 (16.1)	
	Chronic active calculous cholecystitis	6	16.08 ± .49	15.6-16.7 (16)	
	Chronic active cholecystitis	4	15.98 ± .52	15.5-16.6 (15.9)	
	Other	67	16.04 ± 2.17	11-22.6 (16)	
NLR	Chronic cholecystitis	43	1.93 ± .86	.89-4.76 (1.76)	**.001****
	Chronic calculous cholecystitis	67	2.22 ± 1.49	.78-9.92 (1.94)	
	Chronic active calculous cholecystitis	6	5.4 ± 5.09	1.68-15.51 (3.85)	
	Chronic active cholecystitis	4	3.25 ± 1.64	1.56-4.99 (3.22)	
	Other	67	4.57 ± 6.62	.83-35.64 (2.27)	
MLR	Chronic cholecystitis	43	.19 ± .08	.08-.41 (.16)	**.001****
	Chronic calculous cholecystitis	67	.21 ± .1	.08-.77 (.17)	
	Chronic active calculous cholecystitis	6	.54 ± .48	.21-1.51 (.39)	
	Chronic active cholecystitis	4	.24 ± .11	.11-.37 (.24)	
	Other	67	.35 ± .36	.08-2.06 (.23)	
PLR	Chronic cholecystitis	43	118.7 ± 48.69	47.12-337.84 (111.52)	**.007****
	Chronic calculous cholecystitis	67	123.57 ± 36.99	53.2-235.43 (119.13)	
	Chronic active calculous cholecystitis	6	205.44 ± 111.26	118.06-387.36 (150.89)	
	Chronic active cholecystitis	4	151.78 ± 31.64	123.66-187.44 (148)	
	Other	67	178.35 ± 135.24	57.38-741.94 (133.5)	

Abbreviations: MLR, monocyte/lymphocyte; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio.
Kruskall–Wallis test, *$P < .05$, **$P < .01$.

neutrophil values in terms of diagnosis ($P = .012$; $P < .05$). It was determined that the neutrophil value of the chronic cholecystitis group was statistically significantly lower than the values of chronic active calculous cholecystitis and others group ($P = .001$; $P < .01$). Moreover, the neutrophil values of the chronic calculous cholecystitis group were found to be statistically significantly lower than in the chronic active calculous group ($P = .001$; $P < .01$) (Table 1). No statistically significant difference was found between neutrophil values in terms of the presence of cancer and dysplasia ($P > .05$) (Tables 2 and 3).

Lymphocyte

The mean lymphocyte count was 2.24 ± .82 (range, .31-6.37). There was a statistically significant difference between the lymphocyte levels according to the diagnosis ($P = .026$; $P < .05$). The difference between the lymphocyte values in the "others" group and the chronic cholecystitis and chronic calculous cholecystitis groups was found to be statistically significant ($P = .001$; $P < .01$) (Table 1). No statistically significant difference was found between lymphocyte levels in terms of the presence of cancer and dysplasia ($P > .05$) (Tables 2 and 3).

Monocyte

The mean monocyte count was .48 ± .19 (range, .2-1.47). A statistically significant difference was found between monocyte counts in terms of diagnoses ($P = .002$; $P < .01$). The monocyte level of the chronic cholecystitis group was found to be statistically significantly higher than in the chronic active calculous cholecystitis group and the "others" group ($P = .001$; $P < .01$). Moreover, the monocyte level in the chronic calculous cholecystitis group was found to be statistically significantly higher than in the chronic active calculous cholecystitis group and the "others" group ($P = .001$; $P < .01$) (Table 1). No statistically significant difference was found between monocyte levels in terms of the presence of cancer and dysplasia ($P > .05$) (Tables 2 and 3).

Platelets

The mean platelet count was 278.06 ± 81.75 (range, 113-720). Considering the diagnoses, there was no statistically significant difference between the platelet levels ($P > .05$) (Table 1). No statistically significant difference was found between platelet levels in terms of the presence of cancer and dysplasia ($P > .05$) (Tables 2 and 3).

Plateletcrit

The mean PCT value was calculated as .26 ± .08 (range, .1-.67). Examining the diagnoses, it was determined that there was no significant difference between the PCT values ($P > .05$) (Table 1). Moreover, after examining for the presence of cancer and dysplasia, no statistically significant difference was determined between PCT values ($P > .05$) (Tables 2 and 3).

Mean Platelet Volume

The mean MPV value was 9.5 ± 1.09 (range, 7.4-13.2). Considering the diagnoses, there was a statistically significant difference between MPV values ($P = .001$; $P < .01$). The "others" group was found to have statistically significantly lower MPV values when compared with the chronic cholecystitis and chronic calculous cholecystitis groups. The MPV value of the non-cancer and non-dysplasia groups was determined to be statistically significantly higher than in the cancer and dysplasia groups ($P = .013$; $P < .05$), ($P = .030$; $P < .05$) (Tables 2 and 3).

Platelet Distribution Width

The mean PDW value was 16.13 ± 1.65 (range, 11-25.9). Examining the diagnoses, there was no statistically significant difference between PDW values ($P > .05$) (Table 1). There was no statistically significant difference between PDW values in terms of the presence of cancer and dysplasia ($P > .05$) (Tables 2 and 3).

Neutrophil to Lymphocyte Ratio

The mean NLR value was 3.12 ± 4.34 (range, .78-5.64). After examining the diagnoses, a statistically significant difference was found between NLR ratios ($P = .001$; $P < .01$). The NLRs of the chronic cholecystitis and chronic calculous cholecystitis groups were statistically significantly lower than the chronic active calculous cholecystitis group and the "others" group ($P = .001$; $P < .01$) (Table 1). The NLR of the non-cancer and non-dysplasia groups was found to be statistically significantly lower than that of the cancer and dysplasia groups ($P = .003$; $P < .01$), ($P = .027$; $P < .01$) (Tables 2 and 3).

Monocyte to Lymphocyte Ratio

The mean MLR value was .27 ± .25 (range, .08-2.06). The MLRs in the chronic cholecystitis and chronic calculous cholecystitis groups were determined to be lower than in the chronic active calculous cholecystitis group and the "others" group ($P = .001$; $P < .01$) (Table 1). The MLR value of the non-cancer group was significantly lower than in the cancer group ($P = .018$; $P < .05$) (Table 2). The MLR group in the non-dysplasia group was, however, statistically significantly lower than in the dysplasia group ($P = .007$; $P < .05$) (Table 3).

Platelet to Lymphocyte Ratio

The mean PLR value was calculated as 145.31 ± 93.3 (range, 47.12-741.94). After examining the diagnoses, the difference

Table 2. Comparison of Parameters by Diagnosis of Cancer.

		N	Mean ± SD	Min-Max (Median)	*P*
Neutrophil	None	178	5.1 ± 2.6	1.54-19.13 (4.51)	.066
	Yes	9	6.72 ± 3.25	2.5-13.3 (5.59)	
Lymphocyte	None	178	2.26 ± .81	.31-6.37 (2.28)	.055
	Yes	9	1.69 ± .77	.49-3.06 (1.74)	
Monocyte	None	178	.47 ± .19	.2-1.47 (.45)	.071
	Yes	9	.56 ± .18	.24-.91 (.52)	
Platelet	None	178	279.2 ± 82.16	113-720 (270.5)	.311
	Yes	9	255.44 ± 73.69	166-404 (267)	
PCT	None	178	.27 ± .08	.1-.67 (.26)	.090
	Yes	9	.22 ± .06	.13-.32 (.22)	
MPV	None	178	9.54 ± 1.07	7.4-13.2 (9.4)	**.013***
	Yes	9	8.67 ± 1.05	7.47-11 (8.5)	
PDW	None	178	16.12 ± 1.66	11-25.9 (16)	.587
	Yes	9	16.23 ± 1.75	13.3-19.2 (16.2)	
NLR	None	178	3.01 ± 4.28	.78-35.64 (2.02)	**.003****
	Yes	9	5.27 ± 5.06	1.83-17.9 (3.07)	
MLR	None	178	.26 ± .25	.08-2.06 (.19)	**.018***
	Yes	9	.43 ± .32	.13-1.2 (.36)	
PLR	None	178	143.47 ± 93.05	47.12-741.94 (121.11)	.123
	Yes	9	181.68 ± 96.25	103.59-395.92 (133.5)	

Abbreviations: MLR, monocyte/lymphocyte; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio.
Mann–Whitney U test, *$P < .05$, **$P < .01$.

Table 3. Comparison of Parameters by the Diagnosis of Dysplasia.

		N	Mean ± SD	Min-Max (Median)	*P*
Neutrophil	None	136	5 ± 2.66	1.54-19.13 (4.3)	.053
	Yes	51	5.63 ± 2.58	1.86-13 (4.94)	
Lymphocyte	None	136	2.3 ± .78	.49-6.37 (2.28)	.095
	Yes	51	2.05 ± .89	.31-4.2 (2.06)	
Monocyte	None	136	.47 ± .2	.2-1.47 (.45)	.107
	Yes	51	.49 ± .15	.27-.94 (.48)	
Platelet	None	136	275.46 ± 82.5	113-720 (267)	.364
	Yes	51	284.98 ± 80.12	154-471 (282)	
PCT	None	136	.27 ± .08	.1-.67 (.25)	.973
	Yes	51	.26 ± .07	.14-.45 (.26)	
MPV	None	136	9.59 ± 1.02	7.47-12.1 (9.55)	**.030***
	Yes	51	9.26 ± 1.22	7.4-13.2 (9.2)	
PDW	None	136	16.24 ± 1.34	13.3-25.9 (16)	.243
	Yes	51	15.9 ± 2.16	11-21.2 (15.95)	
NLR	None	136	2.51 ± 2.24	.78-17.9 (1.94)	**.027***
	Yes	51	4.75 ± 7.26	.83-35.64 (2.15)	
MLR	None	136	.23 ± .18	.08-1.51 (.18)	**.007****
	Yes	51	.35 ± .38	.08-2.06 (.23)	
PLR	None	136	130.49 ± 54.63	47.12-395.92 (120.66)	.061
	Yes	51	184.83 ± 148.77	57.38-741.94 (134.57)	

Abbreviations: MLR, monocyte/lymphocyte; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; PCT, Plateletcrit; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio.
Mann–Whitney U Test *$P < .05$ **$P < .01$.

between PLR values was statistically significant ($P = .001$; $P < .01$). PLR values in the chronic cholecystitis and chronic calculous cholecystitis groups were significantly lower than in the chronic active calculous cholecystitis group and the "others" group ($P = .001$; $P < .01$) (Table 1). PLR values were statistically significantly different in terms of the presence of cancer and dysplasia ($P > .05$) (Tables 2 and 3).

ROC Analysis

For dysplasia, the optimal cut-off value of NLR was found as 1.61 with respect to the ROC curve (sensitivity = 82.4% and specificity = 66.9%) (Figure 1), the MLR cut-off value was found as .19 (sensitivity = 66.7% and specificity = 55.1%) (Figure 2), and the PLR value was determined as 81.45 (sensitivity = 96.1% and specificity = 87.5%) (Figure 3). Given the results obtained for cancer in the present study, the optimal cut-off value of the NLR value was found as 2.65 (sensitivity = 77.8% and specificity = 83.5%) (Figure 4), for MLR it was .35 (sensitivity = 66.7% and specificity = 89%) (Figure 5), and for PLR, it was 182.69 (sensitivity = 44.4% and specificity = 68.2%) (Figure 6).

Discussion

In our study, with respect to the ROC curve, the optimal cut-off values of NLR, MLR, and PLR for dysplasia were found as 1.61 (sensitivity = 82.4% and specificity = 66.9%), .19 (sensitivity = 66.7% and specificity = 55.1%), and 81.45 (sensitivity = 96.1% and specificity = 87.5%). Dysplasia is the leading precancerous lesion and it is incidentally detected during postoperative histopathologic examinations. For this reason, the present study involves cut-off values of NLR, MLR, and PLR in patients with dysplasia, which, to the best of our knowledge, has not been examined in the literature before. The authors of the present study believe that these cut-off values might be useful in detecting GBCs, which are rarely seen but course lethally, at the early phase or before their development (at the phase of dysplasia).

In the present study, ROC analyses were applied to cancer cases and optimal cut-off values of NLR, MLR, and PLR values were found as 2.65 (sensitivity = 77.8% and specificity = 83.5%), .35 (sensitivity = 66.7% and specificity = 89%), and 182.69 (sensitivity = 44.4% and specificity = 68.2%), respectively. The results obtained here are in parallel with the literature. In a study by Lalosevic et al[17] that examined the diagnostic efficiency for cancer cases, the cut-off values of NLR and PLR were found as 2.15 (AUC = .790, 95% CI: .736-.884, sensitivity = 74% and specificity = 73%) and 123 (AUC = .846, 95% CI: .801-.891, sensitivity = 73.5% and specificity = 80%). Deng et al[6] reported the cut-off values as 145.33 for PLR, 2.6 for NLR, and 2.66 for MLR. Moreover, Zhu et al[18] found the optimum cut-off values of NLR, PLR, and MLR as 3.13, 143.77, and .29, respectively.

Both NLR and PLR are improved variations of rational absolute blood cell counts and they are defined as risk indicators. Among the parameters constituting these ratios, neutrophil and PLT counts are poor prognostic determinants, and lymphocyte counts are accepted to be a good prognostic determinant.[15,16,19] In a study by Azab et al,[15] it was reported that both NLR and PLR were important predictors of mortality in multivariate models. Besides that, analyzing the lymphocyte subgroups, NLR was found to be an important mortality predictor, whereas PDW was not found to be statistically significant, which raises the question as to whether the relationship between this increase and PLR is directed by the PLT count or only the lymphocyte count.[16]

Even though a statistically significant relationship was found between NLR, PLR, and MLR values and dysplasia and cancer in the present study, it was interesting that no relationship was found between neutrophil, lymphocyte, and monocyte counts and dysplasia and cancer ($P > .05$). In a study by Deng et al,[6] high NLR and PLR values were reported to be correlated with poor tumor differentiation. Moreover, advanced TNM phase and high PLR and low LMR values were found to have a statistically significant relationship, whereas MLR levels of patients with advanced T-phase or anemia were found to be statistically significantly lower. In the present study, however, PLT, MLR, and NLR values of patients with tumors were found to have no increase in proportion to the advancing phase. In recent studies, it was claimed that the combined use of abnormal PLT or lymphocyte counts could be useful as a parameter in predicting poor prognosis for GBC.[20] On the other hand, in many previous studies, it was reported that high levels of PLT significantly increased the mortality risk in cancer cases including GBC. As in the present study, Pang et al[3] reported no statistically significant relationship between PLT levels and cancer. Furthermore, a positive correlation was found between increased serum PLT levels and tumor diameter.

In in-vitro environments, the growth and invasion of tumors by a rapid release of PLT occurs via platelet-derived proangiogenic mediators. In the present study, the tumor with the largest diameter (5 cm) was determined to have the highest PLR, NLR, and MLR levels and lowest lymphocyte count. However, in the same case, no parallel correlation was found with PLT levels. In previous studies conducted on cancer, dysplasia, and PLT levels, it was reported that lymphocyte counts lower than 1000/μL were accepted as a poor prognostic factor for GBC. Moreover, it was also determined that lymphocyte count was in negative correlation with the TNM stage.[3] In the present study, the NLR value of the non-cancer and non-dysplasia group was found to be statistically significantly lower than in the cancer and dysplasia group ($P = .003$; $P < .01$), ($P = .027$; $P < .01$). There was no statistically significant difference between PLR values in terms of the presence of cancer and dysplasia ($P > .05$). In the present study, the fact that PLR and PLT values were found to have no

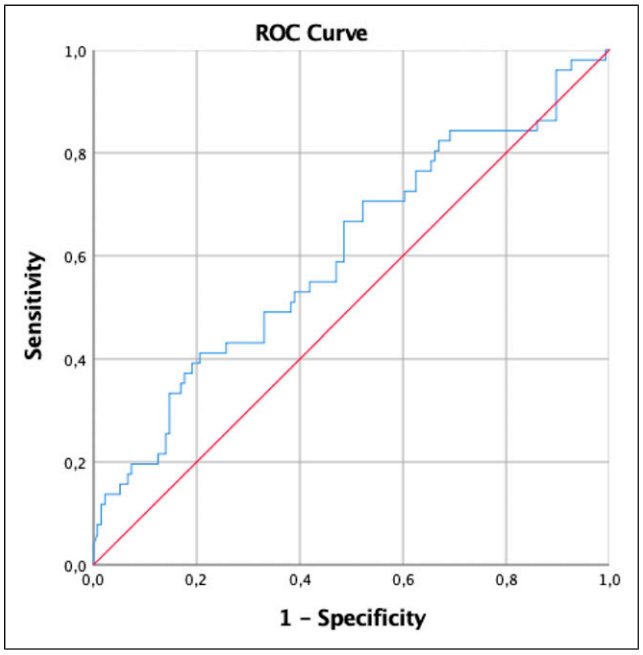

Figure 1. ROC curve of NLR parameter in dysplasia. NLR, neutrophil to lymphocyte ratio; ROC, receiver operating characteristics.

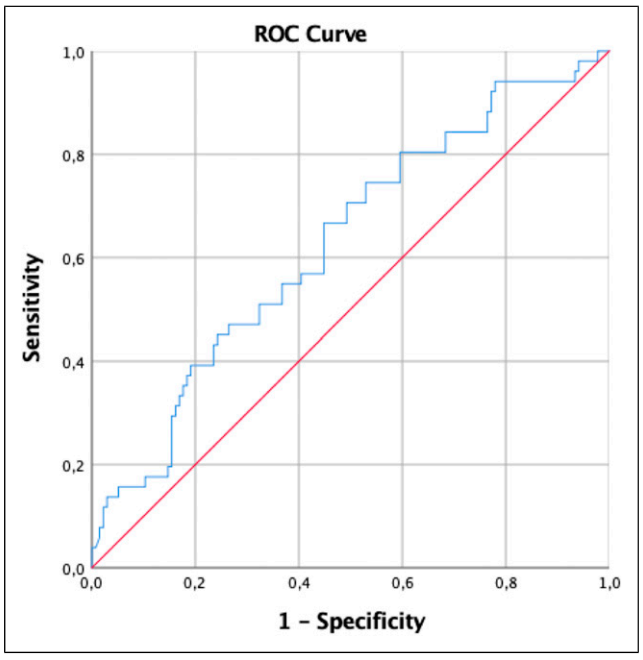

Figure 2. ROC curve of MLR parameter in dysplasia. MLR, monocyte/lymphocyte; ROC, receiver operating characteristics.

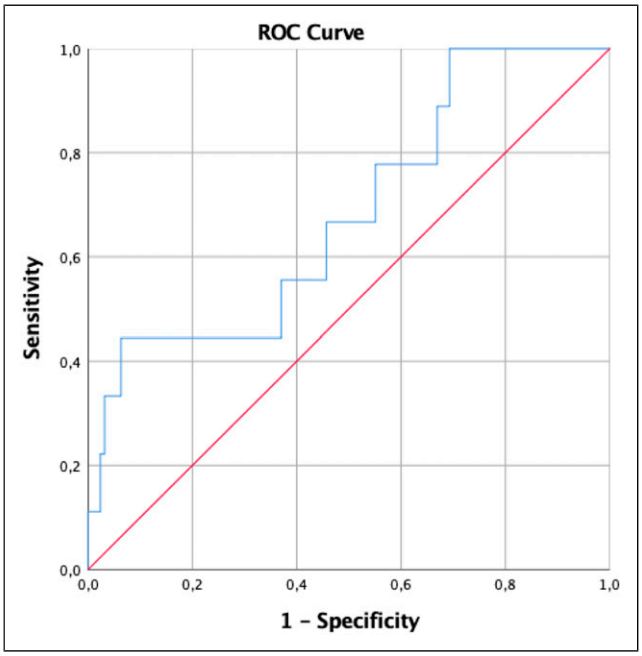

Figure 3. ROC curve of PLR parameter in dysplasia. PLR, platelet to lymphocyte ratio; ROC, receiver operating characteristics.

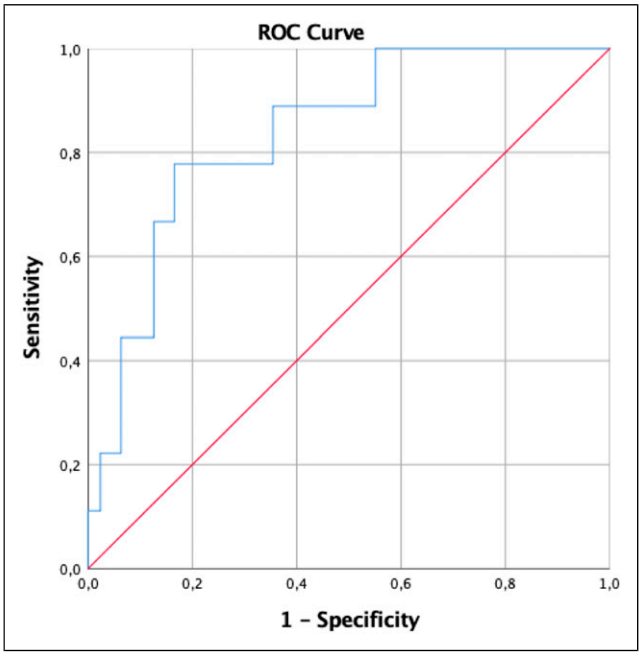

Figure 4. ROC curve of NLR parameter in cancer. NLR, neutrophil to lymphocyte ratio; ROC, receiver operating characteristics.

relationship with cancer and dysplasia suggested that it might be because GBC is not thrombogenic cancer.

Although the prognostic effect of MLR in various types of cancer is known, its prognostic role in GBC has not yet been revealed.[4] In a study by Choi et al, it was reported that MLR was an independent indicator of progression-free survival and overall survival for patients with GBC receiving chemotherapy. In previous studies, it was shown that low MLR values (high LMR values) indicated better survival, whereas high MLR (low LMR) values were related to poor prognosis. Although no exact mechanism explaining the relationship

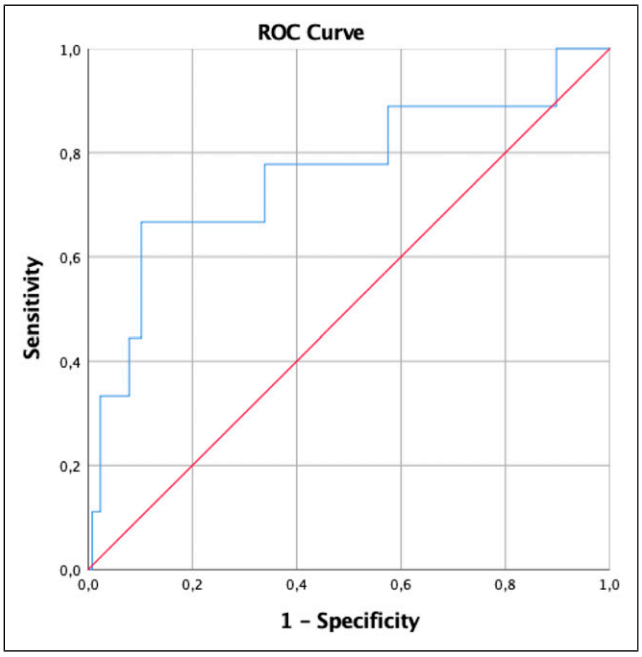

Figure 5. ROC curve of MLR parameter in cancer. MLR, monocyte/lymphocyte; ROC, receiver operating characteristics.

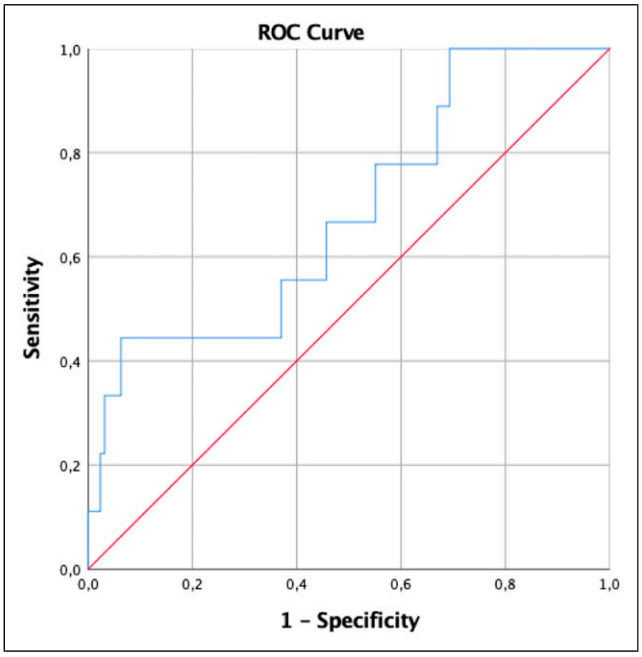

Figure 6. ROC curve of PLR parameter in cancer. PLR, platelet to lymphocyte ratio; ROC, receiver operating characteristics.

between high MLR and poor prognosis has been revealed, it is thought that relatively low lymphocytes and high monocyte counts may play a role.[4,21] Tumor-associated macrophages (TAM) derived from circulating monocytes increase the protumoral functions suppressing the immune reaction against tumor cells, as well as tumor cell migration, invasion, metastasis, and angiogenesis. It is known that peripheral monocyte levels are related to levels of TAM. For this reason, peripheral monocytes increasing with poor prognosis also supports high MLR levels related to poor prognosis.[4,21] In the present study, in parallel with the literature, the MLR values of the non-cancer and non-dysplasia groups were found to be statistically significantly lower than in the cancer and dysplasia groups ($P = .018$; $P < .05$), ($P = .007$; $P < .05$).

Relationship between Platelet Count and Cancer and Cholecystitis

Platelets play an important role in many inflammatory diseases.[3] They tend to aggregate in circulation through homotypical adhesions between tumor cells and heterotypical adhesions and between tumor cells and platelets. This aggregation of platelets and tumor cells may allow tumor cells to survive. Also, platelets release factors that activate angiogenesis, which stimulates tumor progression. According to the study by Azab et al,[15] high platelet counts were related to a higher mortality trend. In the present study, the platelet count was found to range between 113 and 720 and the mean value was 278.06 ± 81.75. No statistically significant relationship was found between cholecystitis subtypes, dysplasia, and cancer ($P > .05$). For this reason, when examining the relationship of PLT counts with diagnosis, evaluating it together with other hematologic parameters (such as PLR) would be useful, especially for patients with normal PLT counts. The use of PLR alters the intravascular fluid component and alleviates the effects of many common parameters such as the platelet count.[14] In the present study, PLR values in chronic cholecystitis and chronic calculous cholecystitis groups were found to be statistically significantly lower than in the chronic active calculous cholecystitis group ($P = .001$; $P < .01$) (Table 1). However, there was no statistically significant difference between PLR values according to the presence of cancer and dysplasia ($P > .05$).

Relationship between Neutrophil Count and Cancer and Cholecystitis

Neutrophils may promote tumor growth and metastasis. Besides increasing the rate of mutagenesis, they also increase the remodeling of the extracellular matrix and the release of reactive oxygen species, nitric oxide, and arginase, suppressing the T-cell response. Granulocytes were also found to proportionally inhibit the function of cytotoxic lymphocytes. In a study by Azap et al,[15] it was reported that a high neutrophil count was related to worse survival in both univariate and multivariate models, and when compared with the absolute neutrophil count, NLR was a superior predictive factor in determining survival rates. Teramukai et al[22] reported that an increase in the neutrophil count was related to a decrease in survival in non-small cell cancer. In the present study, although no significant relationship was found between

neutrophil levels and dysplasia and cancer ($P > .05$), NLR levels in the non-cancer and non-dysplasia group were found to be statistically significantly lower than in the cancer and dysplasia group. Moreover, the tumor with the largest diameter in the present study was found to have the highest neutrophil count ($8.77 \times 10^3/\mu L$).

Relationship between Lymphocyte Value and Cancer

Tumor development and lymphocyte increases play an inhibitory role because lymphocytes regulate the homeostasis of the immune system during chronic inflammation and have an anti-inflammatory effect.[23] Cytotoxic T-lymphocytes (CTLs) induce the apoptosis of cancer cells through the interaction between CD95L molecules (Fas ligand) on CTL and CD95 (Fas) molecules on target cancer cells. In previous studies examining tumor-infiltrating lymphocytes in multivariate models, it was determined that there was a relationship between low peripheral blood lymphocyte counts and low survival.[6,15,23] Gooden et al[24] related the increasing lymphocyte infiltration to good prognosis and better response to treatment among patients with cancer. Again, using univariate and multivariate models, Azab et al[15] reported that patients with high lymphocyte counts had better survival when compared with patients with low lymphocyte counts. Interestingly, no statistically significant relationship was found between lymphocyte levels among patients with cancer and dysplasia in the present study ($P > .05$).

Relationship between PLR, NLR, MLR, and Cholecystitis

The combined use of clinical history, examination findings, imaging methods (especially ultrasonography), and bio-indicators contributes to the accuracy of the diagnosis of acute calculous cholecystitis. The development of complications such as acute cholecystitis, gangrenous cholecystitis, and perforation increases mortality and morbidity, and thus using preoperative inflammatory indicators would be useful in early diagnosis. Morbidity and mortality can be reduced through early surgery. There are no specific imaging diagnostic criteria for non-complicated acute calculous cholecystitis.[25] Moreover, imaging methods are not sensitive enough to detect severe acute cholecystitis. In recent years, it was claimed that neutrophilia and relative lymphopenia might be useful in predicting mild and severe acute cholecystitis. NLR is an easy-to-measure parameter and is a good indicator of inflammation. Many studies reported that high NLRs indicated poor prognosis in patients with cancer, cardiovascular disease, and those receiving intensive care. Moreover, these studies also reported that increasing NLRs provided indications for disease severity, stage of disease, morbidity, and mortality.[25,26]

Leucocytes and PLR are among the well-known hematologic determinants of severe inflammation. Leucocyte counts are a low-cost and useful indicator of inflammation, but they are insufficient for assessing the clinical severity of disease. Ertok et al[26] reported that NLR levels in acute cholecystitis were significantly higher than in chronic cholecystitis. In the present study, it was determined that PLR values in the chronic cholecystitis and chronic calculous cholecystitis groups were statistically significantly lower than in the chronic active calculous cholecystitis group and the "others" group ($P = .001$; $P < .01$). Furthermore, similar to PLR, it was also determined that the MLR values in the chronic cholecystitis and chronic calculous cholecystitis groups were significantly lower than in the chronic active calculous cholecystitis group ($P = .001$; $P < .01$). In the literature, few studies have examined PLR, PLR, and MLR together in acute cholecystitis. The results obtained here about the predictive values of these inflammatory indicators (NLR, PLR, and PLR) are in parallel with and corroborate the well-established relationship between cancer and inflammation.

The present study is believed to contribute to understanding the role of neutrophils, platelets, and monocytes in cancer, and the relationship between lymphocytes, cancer, and inflammation. Besides that, it is thought that NLR and PLR can be used as alternative bio-indicators in determining the stage of inflammation in acute cholecystitis. The objective and reproducible nature of prognostic scores based on systemic inflammation increases the usefulness of such observations. Although there are ethnic differences between normal neutrophil and lymphocyte ranges and the mean NLR value determined in cohort studies was found as 2.15,[27] in the present study, however, the NLR value was found to range between .78 and 35.64 and the mean value was 3.12 ± 4.34. Patients of the same ethnic origin, patients with diabetes and cardiovascular disease, those with a high BMI, and smokers had significantly higher NLR values. For this reason, the abnormal thresholds most widely used for NLR are probably >5 and >3.[26] The results obtained here indicate the importance of the staging of tumors and the host's systemic inflammatory response for patients with operable disease. These indicators can be used as a comparison instrument in both preoperative and follow-up periods for patients with resectable GBC.

Platelet Distribution Width, Plateletcrit, Mean Platelet Volume

The changes in PLT functions and size are related to systemic inflammation, thus it was thought that PDW could be useful for the prognosis of certain diseases. In recent years, studies were conducted on the reactive use of PDW values in acute appendicitis prognosis. In their study, Aydoğan et al[28] reported that PDW was statistically significantly higher in acute appendicitis. Moreover, in a study by Fan et al,[29] the authors reported that PDW was statistically significantly higher in acute gangrenous appendicitis when compared with the control group.[30] In the present study, PDW was found to have no statistically significant relationship with cancer and

dysplasia ($P > .05$). High MPV levels were found to be related to active inflammation, whereas low MPV levels were found to be related to several chronic diseases such as systemic lupus erythematosus and osteoporosis.[13,31] In a study by Sayit et al,[13] it was reported that the MPV values of patients with acute cholecystitis were lower than those of normal individuals. In the present study, the MPV value of the "others" group was statistically significantly lower than in the chronic cholecystitis and chronic calculous cholecystitis groups. Moreover, the MPV values in the non-cancer and non-dysplasia groups were found to be statistically significantly higher than in the cancer and dysplasia groups ($P = .013$; $P < .05$) ($P = .030$; $P < .05$). The results obtained here suggest that MPV is a more useful inflammation indicator for gallbladder pathologies than PDW and PCT.

Data regarding the use of medication including preoperative use of anti-inflammatory therapy and the medical conditions of participants were limited, lacking, or not accessible because the present study was designed as cross-sectional, retrospective, and mono-centric. However, despite the limitations specified above, because the present study examined the hemogram findings in gallbladder pathologies and analyzed cut-off values, especially in patients with dysplasia and cancer, the present study is believed to contribute to the literature.

Conclusion

The present study confirms and supports the use of easy-to-measure and reproducible bio-indicators bringing no additional cost, such as preoperative neutrophil and monocyte counts and NLR, MLR, and PLR ratios in predicting gallbladder pathologies. Moreover, when compared with PLR, NLR and MLR are better indicators in predicting the development of cancer and gallbladder dysplasia. These results suggest that, when compared with PLTs, neutrophils and monocytes can play an important role in promoting and predicting gallbladder pathology, dysplasia, and cancer in the acute phase. Moreover, when examined together with preoperative hemogram findings, the cut-off values of NLR, PLR, and MLR found in patients with dysplasia and cancer in the present study can be used in determining the development and early recurrence of GBC and dysplasia, which is the antecedent of cancer and courses generally asymptomatically with poor prognosis. Moreover, it is also thought that these values can be used as additional useful factors that might affect the surgical and oncologic treatment procedure.

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Declaration of Conflicting Interests

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Ethical Approval

The present study was conducted between July 1st, 2020, and September 1st, 2020, upon the approval (Date: September 09, 2020, No. 53-07-13) of the Non-invasive Clinical Researches Ethical Committee of Uşak University. The study was performed in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was not requested because the study was retrospective and the data were analyzed anonymously.

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