Research Article

Cancer Epidemiology, Biomarkers & Prevention

A High Monocyte-to-Lymphocyte Ratio Predicts Poor Prognosis in Patients with Advanced Gallbladder Cancer Receiving Chemotherapy

Young Hoon Choi[1,2], Jae Woo Lee[3], Sang Hyub Lee[1], Jin Ho Choi[1], Jinwoo Kang[4], Ban Seok Lee[5], Woo Hyun Paik[1], Ji Kon Ryu[1], and Yong-Tae Kim[1]

Abstract

Background: Monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been reported to be prognostic markers in various cancers. However, the prognostic value of these inflammatory biomarkers, particularly MLR, in gallbladder cancer remains to be determined.

Methods: From 2005 to 2016, 178 patients with histologically confirmed gallbladder adenocarcinoma who underwent palliative chemotherapy were queried in this study. The association between survival and various clinical and laboratory variables, including MLR, NLR, and PLR, was investigated. The optimal cutoff values for MLR, NLR, and PLR were determined using the maxstat package of R.

Results: Patients with high MLR (>0.24) were expected to have shorter progression-free survival [PFS; hazard ratio (HR), 2.100; 95% confidence interval (CI), 1.397–3.157; $P < 0.001$] and overall survival (OS; HR, 2.533; 95% CI, 1.664–3.856; $P < 0.001$) compared with patients with low MLR ($\leq$0.24). In multivariate Cox model, CA 19-9, stage, and MLR were independent factors for PFS. MLR was also an independent predictor of OS along with PLR, age, and CA 19-9, whereas NLR was not significantly associated with OS. Time-dependent receiver operating characteristic (ROC) analysis showed that the area under the curve of MLR for predicting OS was greater than that of NLR and PLR at most time points.

Conclusions: MLR independently predicts survival in gallbladder cancer patients undergoing chemotherapy. Future prospective studies are needed to validate its value as a prognostic biomarker.

Impact: MLR is an inexpensive and easily available biomarker for predicting prognosis in patients with gallbladder cancer undergoing chemotherapy.

Introduction

Gallbladder cancer is an uncommon cancer that accounts for 1.3% of the cancer incidence worldwide, but it is the most common cancer of the biliary tract (1, 2). Most patients with gallbladder cancer are diagnosed with advanced disease at the time of diagnosis, and the prognosis is poor with a 5-year survival rate of less than 10% (2, 3).

There is growing evidence that inflammation plays an important role in the development and progression of cancer and that persistent inflammatory responses are associated with poor prognosis (4, 5). Because of this, inflammatory biomarkers such as monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), which can be obtained from the complete blood count, have been studied as prognostic markers in various cancers. As a result, MLR, NLR, and PLR have been associated with prognosis in several solid tumors, including liver, pancreatic, esophageal, and lung cancer (6–9). There are also a few studies showing that NLR and PLR reflect prognosis in biliary tract cancer, including gallbladder cancer (10, 11). However, most studies on NLR and PLR performed only in gallbladder cancer, not in biliary tract cancer, were performed in surgically resected gallbladder cancer, and there were no studies performed in advanced gallbladder cancer alone (11, 12). Moreover, to our knowledge, no studies have been conducted on MLR as a prognostic factor in either gallbladder cancer alone or in biliary cancer, including gallbladder cancer. Therefore, the present study aims to evaluate the prognostic value of MLR, NLR, and PLR in patients with advanced gallbladder cancer.

Materials and Methods

Patients

A total of 178 patients with advanced gallbladder cancer who underwent systemic chemotherapy at the Seoul National University Hospital between January 2005 and December 2016 were enrolled in this study. The inclusion criteria were as follows: (i) histologically confirmed gallbladder adenocarcinoma; (ii) unresectable, locally advanced or metastatic gallbladder cancer; (iii) at least two cycles of chemotherapy. Unresectable, locally advanced or metastatic gallbladder cancer included the following

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea. [2]Division of Gastroenterology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea; Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea. [3]Department of Gastroenterology, Mediplex Sejong Hospital, Incheon, Korea. [4]Department of Internal Medicine, Seoul National University Boramae Hospital, Seoul National University College of Medicine, Seoul, Korea. [5]Department of Internal Medicine, Kang-Il Hospital, Gimhae, Korea.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Sang Hyub Lee, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, 03080, Korea. Phone: 82-2-2072-4892; Fax: 82-2-762-9662; E-mail: gidoctor@snuh.org

Cancer Epidemiol Biomarkers Prev 2019;28:1045–51

doi: 10.1158/1055-9965.EPI-18-1066

cases (13, 14): Distant metastases, including liver metastasis and peritoneal metastasis; metastases to lymph node beyond locoregional lymph nodes (lymph nodes around cystic duct, common bile duct, and hepatoduodenal ligament); extensive involvement of hepatoduodenal ligament; encasement of major vessels, including hepatic artery and portal vein; cases determined to be unresectable by multidisciplinary team, including hepatobiliary surgeons, radiologists, and medical oncologists.

Patients were excluded from the study if they had a history or presence of other malignancy, or had missing follow-up data making it impossible to calculate the progression-free survival (PFS) and overall survival (OS).

Data collection and definition

Demographic and clinical data, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidity, tumor-node-metastasis (TNM) stage (13), biliary decompression, and chemotherapy regimen were obtained from the medical records. Comorbidity was scored using the category of Charlson comorbidity index (15). Age and cancer-related factors were not included in comorbidity scoring and were analyzed as independent variables.

Laboratory data were also obtained at the time of diagnosis of gallbladder cancer, including carbohydrate antigen 19-9 (CA 19-9) and blood counts with differential counts, including neutrophil, lymphocyte, monocyte, and platelet counts.

MLR was defined as the absolute monocyte count divided by the absolute lymphocyte count. Similarly, NLR and PLR were defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count, and the ratio of the absolute platelet count to the absolute lymphocyte count, respectively.

This study protocol was based on the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1608-045-784). Because of the retrospective nature of this study, informed consent was waived.

Statistical analysis

Continuous variables were shown as their median and interquartile range (IQR) whereas categorical variables were reported as the number (%). The cutoff value for the MLR was determined as the value that result of log-rank test for OS between the two groups divided by the cutoff gave the maximum difference (16). The R package "maxstat" (titled as Maximally Selected Rank Statistics) was used for this analysis. The cutoff values for NLR and PLR were determined using the same method. Comparisons of baseline characteristics between groups were performed using independent samples t tests and χ^2 tests as appropriate. Time-dependent receiver operating characteristic (ROC) curves were generated and the areas under the ROC curves (AUC) were compared to determine the discriminating power of MLR, NLR and PLR for predicting OS. We used the R package "time ROC" (titled as Time-Dependent ROC Curve and AUC for Censored Survival Data) for this analysis. OS was calculated from the date of gallbladder cancer diagnosis until the date of death, and PFS was calculated from the first day of chemotherapy until the date of disease progression or death. OS and PFS were assessed using the Kaplan–Meier method and the log-rank test. Univariate and multivariate Cox proportional hazard analyses were performed to determine the independent predictors for PFS and OS. All variables with P values <0.1 in univariate analysis or that can act as a confounder were included in the multivariate analysis. Statistical analyses were performed using SPSS 21.0 (IBM Corporation) and R 3.4.4 (The R Foundation for Statistical Computing). For all tests, a P value of <0.05 was considered statistically significant.

Results

Patient characteristics

During the study period, 257 patients were diagnosed with unresectable, locally advanced or metastatic gallbladder cancer. After excluding patients who were untreated ($n = 45$), received less than 2 cycles of chemotherapy ($n = 23$), had a history of other malignancy ($n = 9$), and had no follow-up data ($n = 2$), a total of 178 patients were included in this study (Fig. 1). As of May 2018, the median follow-up was 8.7 months (range, 2.0–75.6 months).

Baseline characteristics of the study patients are shown in Table 1. Thirty-nine (21.9%) patients were TNM stage IIIB, and 139 (78.1%) patients were stage IV. Biliary drainage was performed in 71 (39.9%) patients. Most patients received gemcitabine-based chemotherapy ($n = 145$, 81.5%). Median PFS and OS were 4.3 and 8.7 months, respectively.

Clinical features according to MLR, NLR, and PLR

The optimal cutoff values of MLR, NLR, and PLR obtained using maximally selected rank statistics were 0.24, 2, and 108, respectively. We divided the patients into higher and lower groups based on these cutoff values, and the patient characteristics of each group are summarized in Table 2. The proportions of males were higher in the high MLR group (60.0% vs. 24.2%, $P < 0.001$) and in the high NLR group (58.5% vs. 37.2%, $P = 0.024$). Patient performance status tended to be worse in the high NLR group compared with the low NLR group (ECOG performance status 0/1/2; 10.4% vs. 37.2%, 74.1% vs. 55.8%, 15.6% vs. 7.0%, $P < 0.001$). There were no differences in patient performance status between subgroups of MLR and PLR. Biliary drainages were performed more frequently in the high NLR group (44.4% vs. 25.6%, $P = 0.028$) and in the high PLR group (44.3% vs. 17.2%, $P = 0.006$). Other clinical characteristics, including age, stage of cancer, tumor marker, and chemotherapy regimen were comparable between the MLR, NLR, and PLR subgroups.

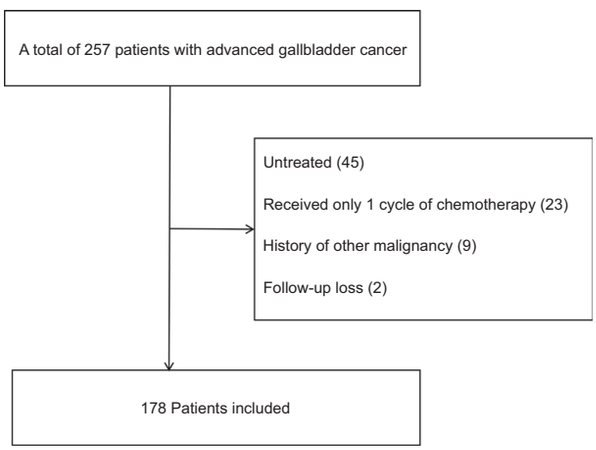

Figure 1.
Flow chart of patient enrollment. This flow chart shows how patients were excluded, and finally how many patients were included in the study.

Table 1. Baseline characteristics of total patients

Characteristics	Median (IQR) or number (%)
Age (y)	64 (58–70)
Sex	
Male	95 (53.4)
Female	83 (46.6)
ECOG Performance status	
0	30 (16.9)
1	124 (69.7)
2	24 (13.5)
Comorbidity score	
0	132 (74.2)
≥1	46 (25.8)
TNM Stage	
IIIB	39 (21.9)
IV	139 (78.1)
Biliary drainage	71 (39.9)
CA 19–9	187 (30–2657)
Chemotherapy regimen	
Gemcitabine based	145 (81.5)
5-Fluorouracil based	33 (18.5)
MLR	0.38 (0.27–0.56)
NLR	3.15 (2.00–5.12)
PLR	175.0 (123.2–250.9)
PFS (months)	4.3 (1.9–7.4)
OS (months)	8.7 (5.9–14.0)

Abbreviations: CA 19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; TNM, tumor–node–metastasis.

Time-dependent ROC analysis for MLR, NLR, and PLR according to OS

The optimal time points for survival analysis to maximize the AUC of MLR, NLR and PLR from time-dependent ROC analysis were 14.7, 14.5, and 6.7 months, respectively. The AUC of MLR for predicting 14.7-month OS was 0.790 [95% confidence interval (CI), 0.691–0.890]. The AUC of NLR for predicting 14.5-month OS and the AUC of PLR for predicting 6.7-month OS were 0.753 (95% CI, 0.635–0.872) and 0.694 (95% CI, 0.579–0.809), respectively (Supplementary Fig. S1).

Factors predicting PFS

Univariate analysis showed that PFS was significantly associated with CA 19-9 >200 U/mL, tumor stage, MLR > 0.24, NLR > 2, and PLR > 108. Multivariate analysis identified three independent factors for poor PFS: MLR > 0.24 [hazard ratio (HR), 2.100; 95% CI, 1.397–3.157; $P < 0.001$), CA 19-9 > 200 U/mL (HR, 1.410; 95% CI: 1.042–1.907; $P = 0.026$) and higher TNM stage (HR, 1.713; 95% CI, 1.178–2.490; $P = 0.005$; Table 3). PFS curve using multivariate Cox proportional hazard model for MLR is shown in Fig. 2A.

Factors predicting OS

In univariate analysis, age >65years, ECOG performance status, CA 19-9 > 200 U/mL, MLR > 0.24, NLR > 2, PLR > 108 showed statistically significant associations with OS. Multivariate analysis revealed that MLR > 0.24 (HR, 2.533; 95% CI, 1.664–3.856; $P < 0.001$), Age > 65 years (HR, 1.506; 95% CI, 1.103–2.056; $P = 0.010$), CA 19–9 > 200 U/mL (HR, 1.680; 95% CI, 1.225–2.305; $P = 0.001$), and PLR > 108 (HR, 1.696; 95% CI, 1.091–2.635; $P = 0.019$) were independent factors for OS (Table 4). OS curve using multivariate Cox proportional hazard model for MLR is shown in Fig. 2B.

Discussion

MLR is known to be a prognostic factor in several types of cancers. However, the prognostic role of MLR in gallbladder cancer remains unknown. In this study, we demonstrated that MLR was an independent indicator of PFS and OS in patients with gallbladder cancer receiving chemotherapy. To the best of our knowledge, this is the first study of MLR as a prognostic factor in gallbladder cancer. In addition, this is the first study of NLR and PLR performed only in patients with advanced gallbladder cancer who received chemotherapy, showing that PLR is an independent factor for OS.

Inflammation is critical in tumor development, growth, invasion, and metastasis (4, 5, 17). In this regard, inflammatory indicators such as NLR and PLR are known to be associated with the prognosis of several tumors, including biliary tract cancer. Cho and colleagues (10) reported that NLR and PLR were independent prognostic factors for OS in patients with biliary tract cancer and Zhang and colleagues (11) reported that NLR was significantly associated with 5-year survival of patients with gallbladder cancer. Our research also showed that NLR and PLR were significantly associated with PFS and OS in univariate analysis, but in multivariate analysis, only PLR was an independent factor for OS. This result differed somewhat from previous studies in that NLR did not reflect OS. The reason for this is unclear, but similar results are seen in studies analyzing NLR, PLR, and LMR together in other cancers. Yang and colleagues (18) reported that LMR was an independent prognostic factor for OS in patients with hepatocellular carcinoma undergoing liver resection, and that NLR and PLR were not independent factors for OS. Similar to our study, Yang and colleagues also showed that NLR and PLR were significant factors in univariate analysis but not in multivariate analysis. The cutoff value of LMR in that study was 4.01, which was similar to the cutoff value of 4.1 when MLR is converted to LMR in our study. In addition, Peng and colleagues (19) reported that LMR was an independent predictor of relapse-free survival and OS in patients with colorectal cancer with liver-only metastases, and that NLR and PLR were not prognostic factors.

Our study also demonstrated that, compared with NLR and PLR, MLR was a superior predictor of OS in patients with gallbladder cancer receiving chemotherapy, showing greater AUC for predicting OS at most time points, especially after 7.4-months. This result was also consistent with studies by Yang and colleagues and Peng and colleagues (18, 19). All of these studies, including ours, showed that low MLR (high LMR) reflects better survival while high MLR (low LMR) was an independent predictor of poor prognosis.

The precise mechanism by which high MLR indicates poor outcome remains unclear, but previous studies have suggested that a relatively lower number of lymphocytes and an excess of monocytes may play an important role. Lymphocytes are a major component of the antitumor defense (20). In particular, tumor infiltrating lymphocytes play a critical role by inducing cancer cell apoptosis through the interaction of $CD4^+$ and $CD8^+$ T-lymphocytes (21, 22). Indeed, tumor infiltrating lymphocytes are associated with favorable prognosis in various cancers (23–25). In contrast, a low lymphocyte count could be responsible for an insufficient immune response in a number of cancers, which would lead to inferior survival (26, 27). This is one of the foundations of inflammatory markers such as NLR and PLR in addition to MLR.

Table 2. Clinical characteristics of the patients according to MLR, NLR, and PLR

	MLR			NLR			PLR		
Characteristics	**≤0.24 *n* = 33, median (IQR) or *n* (%)**	**>0.24 *n* = 145, median (IQR) or *n* (%)**	***P***	**≤2 *n* = 43, median (IQR) or *n* (%)**	**>2 *n* = 135, median (IQR) or *n* (%)**	***P***	**≤108 *n* = 29, median (IQR) or *n* (%)**	**>108 *n* = 149, median (IQR) or *n* (%)**	***P***
Age (y)	62 (56–69)	64 (59–71)	0.381	63 (56–69)	65 (58–71)	0.282	65 (60–73)	64 (58–70)	0.421
Sex			<0.001			0.015			0.536
Male	8 (24.2)	87 (60.0)		16 (37.2)	79 (58.5)		17 (58.6)	78 (52.3)	
Female	25 (75.8)	58 (40.0)		27 (62.8)	56 (41.5)		12 (41.4)	71 (47.7)	
ECOG PS			0.183			<0.001			0.332
0	9 (27.3)	21 (14.5)		16 (37.2)	14 (10.4)		7 (24.1)	23 (15.4)	
1	21 (63.6)	103 (71.0)		24 (55.8)	100 (74.1)		20 (69.0)	104 (69.8)	
2	3 (9.1)	21 (14.5)		3 (7.0)	21 (15.6)		2 (6.9)	22 (14.8)	
Comorbidity score			0.120			0.398			0.819
0	28 (84.8)	104 (71.7)		34 (79.1)	98 (72.6)		22 (75.9)	110 (73.8)	
≥1	5 (15.2)	41 (28.3)		9 (20.9)	37 (27.4)		7 (24.1)	39 (26.2)	
TNM Stage			0.197			0.275			0.419
IIIB	10 (30.3)	29 (20.0)		12 (27.9)	27 (20.0)		8 (27.6)	31 (20.8)	
IV	23 (69.7)	116 (80.0)		31 (72.1)	108 (80.0)		21 (72.4)	118 (79.2)	
Biliary drainage	10 (30.3)	61 (42.1)	0.213	11 (25.6)	60 (44.4)	0.028	5 (17.2)	66 (44.3)	0.006
CA 19-9	146.0 (26.5–763.0)	238.0 (33.0–2657.0)	0.467	79.8 (14.0–990.0)	251.0 (40.1–2700.0)	0.250	83.0 (19.9–824.0)	221.0 (34.0–3215.0)	0.604
Chemotherapy regimen			0.662			0.172			0.396
Gemcitabine based	26 (78.8)	119 (82.1)		32 (74.4)	113 (83.7)		22 (75.9)	123 (82.6)	
5-Fluorouracil based	7 (21.2)	26 (17.9)		11 (25.6)	22 (16.3)		7 (24.1)	26 (17.4)	

Abbreviations: CA 19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PS, performance status; TNM, tumor–node–metastasis.

Table 3. Univariate and multivariate Cox proportional hazard analysis of factors associated with progression-free survival

	Univariate		Multivariate	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age (y)				
≤65	1.00			
>65	1.256 (0.931–1.696)	0.136		
Sex				
Male	1.00			
Female	0.820 (0.609–1.106)	0.193		
ECOG PS		0.233		
0	1.00			
1	1.276 (0.854–1.906)	0.235		
2	1.593 (0.929–2.732)	0.091		
Comorbidity score				
0	1.00			
≥1	0.960 (0.685–1.346)	0.813		
Biliary drainage				
No	1.00			
Yes	1.047 (0.773–1.418)	0.768		
CA 19–9 (U/mL)				
≤200	1.00			
>200	1.480 (1.085–2.018)	0.013	1.410 (1.042–1.907)	0.026
Stage				
IIIB	1.00			
IV	1.838 (1.268–2.664)	0.001	1.713 (1.178–2.490)	0.005
Chemotherapy regimen				
Gemcitabine based	1.00			
5-Fluorouracil based	1.063 (0.723–1.561)	0.757		
MLR				
≤0.24	1.00			
>0.24	2.164 (1.441–3.250)	<0.001	2.100 (1.397–3.157)	<0.001
NLR				
≤2	1.00			
>2	1.447 (1.022–2.050)	0.037		
PLR				
≤108	1.00			
>108	1.464 (0.973–2.204)	0.068		

Abbreviations: CA 19–9, carbohydrate antigen 19–9; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TNM, tumor–node–metastasis.

Monocytes also play an important role in malignancies. Tumor-associated macrophages(TAM) that originate, from circulating monocytes enhance protumoral functions, including tumor cell migration, invasion, metastasis, and angiogenesis, and suppress the immune reaction against tumor cells (17, 28–30). Several studies have reported that increased levels of TAMs reflect poor prognosis in cancer patients (31–33). The level of peripheral monocytes is known to be associated with the level of TAMs (34). Thus, increased peripheral monocytes may also reflect poor prognosis, which supports the result that high MLR indicates poor outcome.

This study has several limitations. First, the current study is based on retrospective data from a single institution. Second, we used only the baseline value of MLR rather than the dynamic change in MLR. In addition, various factors, including other disease conditions and medications, that may affect MLR, were

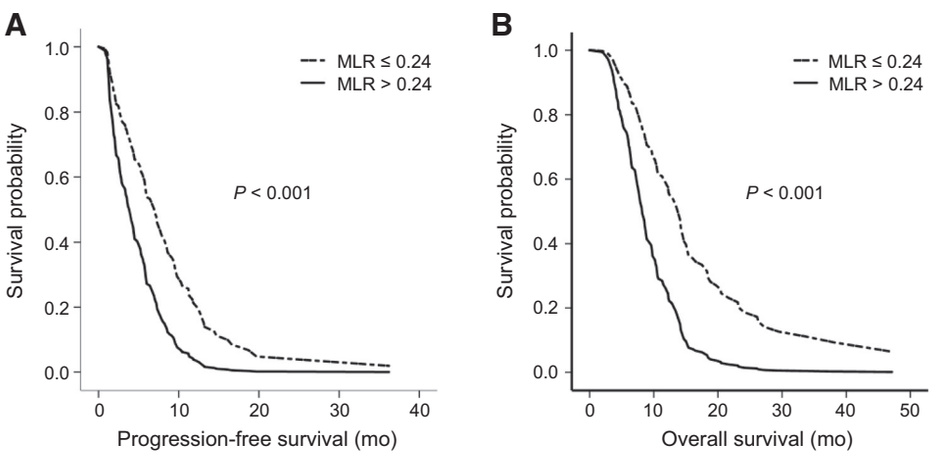

Figure 2.
Survival outcomes according to MLR. PFS and OS were evaluated using multivariate Cox proportional hazard model. Multivariable adjusted PFS (**A**) and OS (**B**) curves for MLR are shown.

Table 4. Univariate and multivariate Cox proportional hazard analysis of factors associated with overall survival

	Univariate		Multivariate	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age (y)				
≤65	1.00			
>65	1.392 (1.028–1.883)	0.032	1.506 (1.103–2.056)	0.010
Sex				
Male	1.00			
Female	0.829 (0.614–1.121)	0.224		
ECOG PS		0.029		
0	1.00			
1	1.284 (0.850–1.939)	0.236		
2	2.083 (1.200–3.614)	0.009		
Comorbidity score				
0	1.00			
≥1	1.080 (0.768–1.518)	0.659		
Biliary drainage				
No	1.00			
Yes	1.182 (0.871–1.604)	0.283		
CA 19–9 (U/mL)				
≤200	1.00			
>200	1.682 (1.226–2.308)	0.001	1.680 (1.225–2.305)	0.001
Stage				
IIIB	1.00			
IV	1.329 (0.923–1.913)	0.126		
Chemotherapy regimen				
Gemcitabine based	1.00			
5-Fluorouracil based	0.923 (0.623–1.357)	0.684		
MLR				
≤0.24	1.00			
>0.24	2.484 (1.652–3.736)	<0.001	2.533 (1.664–3.856)	<0.001
NLR				
≤2	1.00			
>2	2.061 (1.437–2.956)	<0.001		
PLR				
≤108	1.00			
>108	1.900 (1.243–2.904)	0.003	1.696 (1.091–2.635)	0.019

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TNM, tumor–node–metastasis.

not considered. Nevertheless, this study is the first to demonstrate that baseline MLR is a prognostic indicator for patients with gallbladder cancer, and further validation through a well-designed prospective study is warranted.

In conclusion, our study showed that MLR was an independent predictor of PFS and OS in patients with gallbladder cancer undergoing chemotherapy. If these results are validated, MLR can be used as a valuable biomarker for prognosis prediction in gallbladder cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.H. Lee, B.S. Lee, J.K. Ryu, Y.-T. Kim
Development of methodology: Y.H. Choi, J.W. Lee, S.H. Lee
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y.H. Choi, J.W. Lee, J.H. Choi, J. Kang, J.K. Ryu, Y.-T. Kim
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y.H. Choi, J.W. Lee, J.H. Choi, J. Kang, J.K. Ryu, Y.-T. Kim
Writing, review, and/or revision of the manuscript: Y.H. Choi, S.H. Lee, W.H. Paik, J.K. Ryu, Y.-T. Kim
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.W. Lee, J.H. Choi, J.K. Ryu, Y.-T. Kim
Study supervision: S.H. Lee, B.S. Lee, J.K. Ryu, Y.-T. Kim

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 2, 2018; revised November 26, 2018; accepted February 25, 2019; published first March 6, 2019.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
2. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014;6:99–109.
3. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol 2003;4:167–76.
4. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493–503.

5. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
6. Xiao WK, Chen D, Li SQ, Fu SJ, Peng BG, Liang LJ. Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. BMC Cancer 2014;14:117.
7. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 2013;109: 416–21.
8. Zhang X, Wang Y, Zhao L, Sang S, Zhang L. Prognostic value of platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. Int J Biol Markers 2018:1724600818766889.
9. Chen YM, Lai CH, Chang HC, Chao TY, Tseng CC, Fang WF, et al. Baseline and trend of lymphocyte-to-monocyte ratio as prognostic factors in epidermal growth factor receptor mutant non-small cell lung cancer patients treated with first-line epidermal growth factor receptor tyrosine kinase inhibitors. PLoS One 2015;10:e0136252.
10. Cho KM, Park H, Oh DY, Kim TY, Lee KH, Han SW, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer. Oncotarget 2017;8:2329–41.
11. Zhang Y, Jiang C, Li J, Sun J, Qu X. Prognostic significance of preoperative neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients with gallbladder carcinoma. Clin Transl Oncol 2015;17:810–8.
12. Zhang L, Wang R, Chen W, Xu X, Dong S, Fan H, et al. Prognostic significance of neutrophil to lymphocyte ratio in patients with gallbladder carcinoma. HPB (Oxford) 2016;18:600–7.
13. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
14. Lee SE, Kim KS, Kim WB, Kim IG, Nah YW, Ryu DH, et al. Practical guidelines for the surgical treatment of gallbladder cancer. J Korean Med Sci 2014;29:1333–40.
15. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51.
16. Lausen B, Schumacher M. Maximally selected rank statistics. Biometrics 1992:73–85.
17. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.
18. Yang YT, Jiang JH, Yang HJ, Wu ZJ, Xiao ZM, Xiang BD. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival compared to established biomarkers in HCC patients undergoing liver resection. Sci Rep 2018;8:2535.
19. Peng J, Li H, Ou Q, Lin J, Wu X, Lu Z, et al. Preoperative lymphocyte-to-monocyte ratio represents a superior predictor compared with neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for colorectal liver-only metastases survival. Onco Targets Ther 2017;10:3789–99.
20. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004;21:137–48.
21. Pages F, Galon J, Dieu-Nosjean MC, Tartour E, Sautes-Fridman C, Fridman WH. Immune infiltration in human tumors: a prognostic factor that should not be ignored. Oncogene 2010;29:1093–102.
22. Rosenberg SA. Progress in human tumour immunology and immunotherapy. Nature 2001;411:380–4.
23. Goeppert B, Frauenschuh L, Zucknick M, Stenzinger A, Andrulis M, Klauschen F, et al. Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. Br J Cancer 2013;109:2665–74.
24. Santoiemma PP, Powell DJ Jr. Tumor infiltrating lymphocytes in ovarian cancer. Cancer Biol Ther 2015;16:807–20.
25. Fukunaga A, Miyamoto M, Cho Y, Murakami S, Kawarada Y, Oshikiri T, et al. CD8+ tumor-infiltrating lymphocytes together with CD4+ tumor-infiltrating lymphocytes and dendritic cells improve the prognosis of patients with pancreatic adenocarcinoma. Pancreas 2004;28: e26–31.
26. Hoffmann TK, Dworacki G, Tsukihiro T, Meidenbauer N, Gooding W, Johnson JT, et al. Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. Clin Cancer Res 2002;8:2553–62.
27. Vayrynen JP, Tuomisto A, Klintrup K, Makela J, Karttunen TJ, Makinen MJ. Detailed analysis of inflammatory cell infiltration in colorectal cancer. Br J Cancer 2013;109:1839–47.
28. Franklin RA, Liao W, Sarkar A, Kim MV, Bivona MR, Liu K, et al. The cellular and molecular origin of tumor-associated macrophages. Science 2014;344: 921–5.
29. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006;124:263–6.
30. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer 2004;4:71–8.
31. Di Caro G, Cortese N, Castino GF, Grizzi F, Gavazzi F, Ridolfi C, et al. Dual prognostic significance of tumour-associated macrophages in human pancreatic adenocarcinoma treated or untreated with chemotherapy. Gut 2016;65:1710–20.
32. Ishigami S, Natsugoe S, Tokuda K, Nakajo A, Okumura H, Matsumoto M, et al. Tumor-associated macrophage (TAM) infiltration in gastric cancer. Anticancer Res 2003;23:4079–83.
33. Lin JY, Li XY, Tadashi N, Dong P. Clinical significance of tumor-associated macrophage infiltration in supraglottic laryngeal carcinoma. Chin J Cancer 2011;30:280–6.
34. Shibutani M, Maeda K, Nagahara H, Fukuoka T, Nakao S, Matsutani S, et al. The peripheral monocyte count is associated with the density of tumor-associated macrophages in the tumor microenvironment of colorectal cancer: a retrospective study. BMC Cancer 2017;17:404.