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Research Article

The Effect of Monocyte Count on Disease-free Survival in Esophageal Cancer Patients

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Abstract

Objectives: Inflammation plays a pivotal role in cancer development and prognosis. Peripheral blood test is a useful parameter in the evaluation of systemic inflammatory response. The previous studies have shown a relationship between monocyte count and prognosis in some solid tumors. The aim of this study was to evaluate the relationship between the monocyte count assessed at diagnosis and disease-free survival (DFS) on prognosis in patients with esophageal cancer.

Methods: The retrospective study included 145 patients with esophageal cancer who presented to Van Training and Research Hospital Medical Oncology outpatient clinic between January 2015 and September 2020. The effect of monocyte count assessed in the blood samples taken at the time of diagnosis before the initiation of the treatment on DFS was investigated.

Results: The receiver operating characteristics curve analysis determined a cutoff value of 515/μL for the monocyte count assessed at the time of diagnosis. DFS was 17.3 months (95% CI: 8.4–26.2) in patients with a monocyte count ≥515/μL as opposed to 38.5 months (95% CI: 28. 8–48.1) in patients with a monocyte count <515/μL. Moreover, low monocyte count at diagnosis was associated with significantly higher DFS (p<0.001).

Conclusion: It is considered that the proportional distribution of cells in peripheral blood count may reflect the severity of inflammation in the tumor microenvironment. Tumor-associated macrophages are a well-known component of the inflammatory infiltrate in the tumor microenvironment, originating from monocytes. Our findings showed that monocyte count is a prognostic factor affecting DFS in patients with esophageal cancer, regardless of histological subtype.

Keywords: Disease-free survival, esophageal cancer, monocyte count, tumor associated macrophages

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Esophageal cancer is a cancer with a high mortality rate, ranking sixth in cancer-related deaths in the world. Esophageal cancer remains a cancer type with a poor prognosis due to various reasons including late diagnosis, rapid tumor growth, and high recurrence rates.[1–3] Despite advancements in current multimodal treatments such as chemotherapy, radiotherapy, and surgery, 5-year survival rates are still around 30%.[4] Significant parameters used in the determination of the prognosis and survival of esophageal cancer include tumor stage, surgical margin, and metastatic lymph node status. Due to the high mortality rate of esophageal cancer, exploration of new prognostic biomarkers for this tumor is of paramount importance. Accumulating evidence shows that in addition to the characteristics of the tumor, the immune response of the patient is also highly important for determining the prognosis. Moreover, the immune system plays a role in both destroying cancer cells and creating a suitable microenvironment for the pro-

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liferation of cancer cells.[5] The tumor microenvironment typically consists of host components including chronic inflammatory cells, stromal cells, growing vascular cells, and inflammatory infiltrate. This microenvironment is considered to play an important role in cancer development and behavior. Monocyte, an element of the immune system, is a heterogeneous cell showing different responses to different stimuli. Tumor-associated macrophages (TAMs) are a well-known component of the inflammatory infiltrate in the tumor microenvironment, originating from monocytes. TAMs are known to play an important role in tumor angiogenesis and growth. In addition, studies have shown a positive correlation between the monocyte count in peripheral blood and the density of TAMs in the tumor microenvironment.[6] On the other hand, it is known that the differentiation of monocytes into TAMs is in direct relationship with the severity of prognosis and clinical outcomes. Given that the monocyte count at the time of diagnosis dynamically reflects the systemic inflammatory response to cancer, studies often measure monocyte count at the time of diagnosis in their patients. In addition, there are studies supporting the use of monocyte count to predict disease-free survival (DFS) in patients with different types of carcinoma, such as lung adenocarcinoma,[7] hepatocellular carcinoma,[8] prostate cancer,[9] and hematological malignancies.[10] In the present study, we aimed to investigate whether the monocyte count measured at the time of diagnosis can be used as a new prognostic biomarker in predicting DFS in patients with esophageal cancer.

Methods

Patient Selection

The retrospective study included 145 patients with esophageal cancer who presented to Van Training and Research Hospital Medical Oncology outpatient clinic between January 2018 and September 2020. Demographic characteristics (age at diagnosis and gender) and tumor characteristics (tumor stage at diagnosis, tumor location, histological subtype, and hemoglobin, platelet, neutrophil, lymphocyte, and monocyte counts) were recorded for each patient. Complete blood count values that were calculated from peripheral blood samples taken after the establishment of the diagnosis of esophageal cancer were taken as the basis for the examination. The eighth TNM staging system was utilized in determining the stage of patients. The clinical stage of patients was determined by endoscopy, computerized tomography, and PET/CT on some patients. We do not routinely use the endoscopic ultrasound for staging at our hospital. Performance status of the patients at the time of diagnosis was assessed using the Eastern Cooperative Oncology Group (ECOG) scale. The exclusion criteria were set as follows: Secondary malignancy ,tumor infiltration into gastric cardia, symptomatic coronary artery disease, Child-Pugh B or C cirrhosis, chronic respiratory failure, and ECOG 3–4 performance status. The study was approved by Van Training and Research Hospital Ethics Committee.

Blood Tests

Venous blood samples were analyzed using the Sysmex Automated Hematology Analyzer (Sysmex, Kobe, Japan).

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages (%). Normally distributed continuous variables were presented as mean and standard deviation and non-normally distributed continuous variables were presented as median, minimum, and maximum values. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cutoff value for monocyte count. Pearson's Chi-square test was used for the comparison of the two groups that were defined according to the monocyte cutoff value. Post hoc analysis was performed using Bonferroni correction. DFS was determined using the Kaplan-Meier curve. In univariate and multivariate analyses that were conducted to determine the factors affecting survival, comparisons were performed using Cox proportional hazards regression models. $P<0.05$ was considered significant.

Results

Table 1 presents demographic and clinical characteristics of the patients. Median age was 60 (range, 29–87) years and 60% of the patients were female. Most common histological subtype was squamous cell carcinoma (SCC) (n=125; 86.2%), followed by adenocarcinoma (n=19; 13.1%), and mucoepidermoid carcinoma (n=1; 0.7%). In terms of tumor location, 10 (6.9%) cases were cervical, 56 (38.6%) cases were thoracic, 57 (39.3%) cases were distal, and 22 (15.2%) patients had a tumor that originated from thoracic esophagus and extended along the entire distal esophagus. Of all, 8 (5.5%) cases were in the early stage (T1-2 N0 M0), 37 (25.5%) were in the locally advanced stage without lymph node involvement (T3-4 N0 M0), 82 (56.6%) were in the locally advanced stage with lymph node involvement (AnyT N+ M0), and 18 (12.4%) were in the metastatic (M1) stage. At the time of diagnosis, median hemoglobin level was 13.8 (range, 8.9–18.8) g/dL, median platelet count was 276 (range, 110–527) $\times 10^3$/μL, median lymphocyte count was 1926 (range, 254–4100) /μL, median monocyte count was 520 (range, 200–1410)/μL, and median neutrophil count

Table 1. Demographic and clinicopathologic characteristics of the patients

Gender	n	%
Male	58	40.0
Female	87	60.0
Age		
Median	60	
Tumor localization		
Cervical	10	6.9
Thoracic	56	38.6
Distal	57	39.3
Thoracic to Distal	22	15.2
Stage		
T1-2 N0 M0	8	5.5
T3-4 N0 M0	37	25.5
AnyT N+ M0	82	56.6
M1	18	12.4
Pathologic type		
Adenocarcinoma	19	13.1
Squamous cell carcinoma	125	86.2
Mucoepidermoid carcinoma	1	0.7
ECOG[a]		
ECOG-0	63	43.4
ECOG-1	72	49.7
ECOG-2	10	6.9
Monocyte Count		
<515/μL	80	55.2
≥515/μL	65	44.8
Lymphocyte Count		
Mean ± SD, $\times 10^9$/L	1.9±0.6	
Neutrophil Count		
Mean ± SD, $\times 10^9$/L	5.5±0.3	
Platelet Count		
Mean ± SD, $\times 10^3$/μL	276±1.7	
Hemoglobin		
<12g/dL	17	11.7
≥12g/dL	128	88.3

[a]ECOG, The Eastern Cooperative Oncology Group.

Table 2. Clinical characteristics according to the monocyte count in patients with esophageal carcinoma

	Monocyte Count <515	Monocyte Count ≥515/μL	
	n (%)	n (%)	p-value X^2
Age			
<60	42 (59.2)	29 (40.8)	0.345
≥60	38 (51.4)	36 (48.6)	0.892
Gender			
Female	54 (62.1)	33 (37.9)	0.041
Male	26 (44.8)	32 (55.2)	4.183
Stage			
cT1-2 N0 M0	6 (75.0)	2 (25.0)	0.168
cT3-4 N0 M0	22 (59.5)	15 (40.5)	5.046
AnyT N+ M0	46 (56.1)	36 (41.9)	
AnyT AnyN M1	6 (33.3)	12 (66.7)	
ECOGa			
ECOG-0	36 (57.1)	27 (42.9)	0.835
ECOG-1	38 (52.8)	34 (47.2)	0.360
ECOG-2	6 (60.0)	4 (40.0)	
Tumor localization			
Cervical	8 (80.0)	2 (20.0)	0.009
Thoracic	35 (62.5)	21 (37.5)	11.546
Distal	22 (38.6)	35 (61.4)	
Thoracic to Distal	15 (68.2)	7 (31.8)	
Pathologic type			
Adenocarcinoma	8 (42.1)	11 (57.9)	0.323
Squamous cell carcinoma	71 (56.8)	54 (43.2)	2.258
Mucoepidermoid carcinoma	1 (100.0)	0	
Hemoglobin			
Hemoglobin ≥12g/dL	71 (55.5)	57 (44.5)	0.844
Hemoglobin <12g/dL	9 (52.9)	8 (47.1)	0.039

[a]ECOG, The Eastern Cooperative Oncology Group.

was 5557 (range, 1020–45070)/μL. ECOG status was 0 in 63 (43.4%), 1 in 72 (49.7%), and 2 in 10 (6.9%) patients.

In the ROC curve analysis, the optimal cutoff value for monocyte count was determined as 515/μL. At this value, the area under the ROC curve (AUC) was 0.682 (95% confidence interval [CI] 0.58–0.77; p=0.001), with a sensitivity of 67.5% and a specificity of 63.8% (Fig. 1). Table 2 compares the characteristics of the patient groups formed according to the monocyte cutoff value. Monocyte count was lower than the cutoff value in 8 (80%) patients with cervical esophageal cancer, in 35 (62.5%) patients with thoracic esophageal cancer, and in 15 (68.2%) patients who had a tumor that originated from thoracic esophagus and extended along the entire distal esophagus. By contrast, monocyte count was higher than the cutoff value in 35 (61.4%) patients with distal esophageal cancer (p=0.009). Moreover, monocyte count was lower than the cutoff value in 71 (56.8%) patients with SCC, while it was higher than the cut-off value in 11 (57.9%) patients with adenocarcinoma. Recurrence occurred in 13 (16.2%) out of 80 patients with a monocyte count <515/μL and in 27 (41.5%) out of 65 patients with a monocyte count ≥515/μL. The 1-year DFS rate was 60% and the 5-year DFS rate was 33.2%. The estimated mean DFS rate was 29.2 months (95% CI: 21.7–36.7), which was 17.3 months (95% CI: 8.4–26.2) in patients with a monocyte count ≥515/μL as opposed to 38.5 months (95% CI: 28.8–48.1%) in patients with a monocyte count <515/

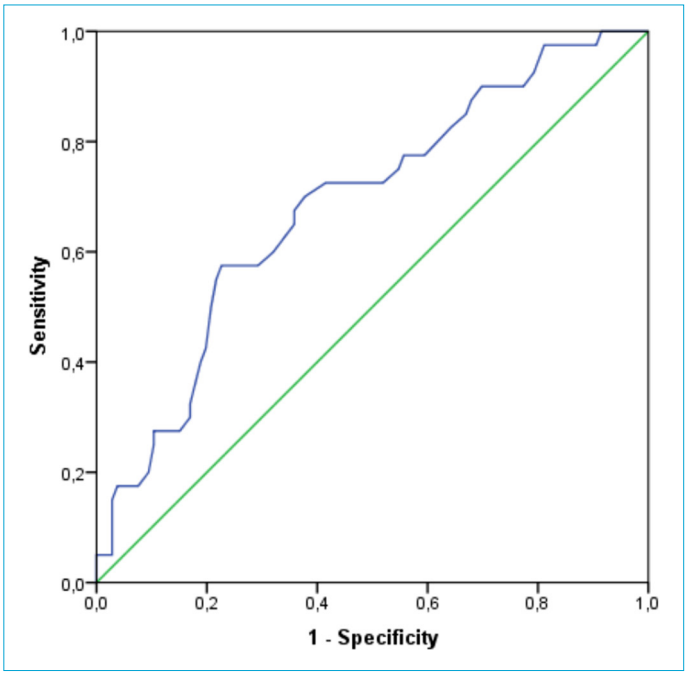

Figure 1. The results of a receiver opearting characteristic curve analysis of the monocyte count in patients with esophageal cancer.

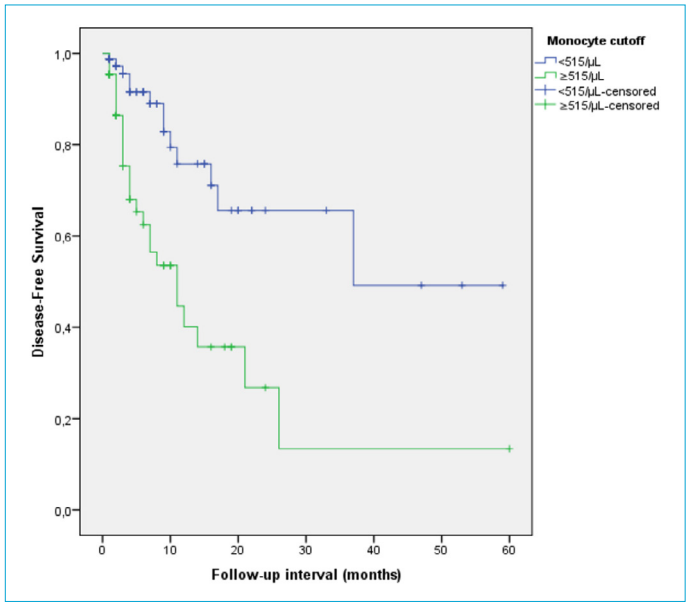

Figure 2. Kaplan–Meier survival curves of disease-free survival in patients with esophageal cancer classified into two groups according to monocyte count.

µL (p<0.001) (Fig. 2). In univariate analysis, that examined the relationship between clinical and biological characteristics of patients and their DFS rates, presence of metastatic disease (p<0.001), monocyte count >515/µL (p<0.001), and ECOG score 1–2 (p=0.033) were significantly associated with disease recurrence. In multivariate analysis, presence of metastatic disease (p=0.007), monocyte count >515/µL (p=0.005), and ECOG score 1-2 (p=0.049) were found to be significant independent risk factors for disease recurrence (Table 3).

Discussion

In the present study, monocyte count, presence of metastatic disease, and ECOG score 1–2 were found to be prognostic factors affecting DFS in patients with esophageal cancer. Similarly, numerous studies have also shown that the presence of metastatic disease and high ECOG performance scores are associated with poor prognosis.[11] On the other hand, monocyte count was found to be effective on DFS, which implicates that monocyte count could be a new prognostic biomarker. Recent studies have shown a strong association between cancer and inflammation. Of note, accumulating evidence suggests that some cells and secreted cytokines involved in cancer-related inflammation have a critical role in tumor development, progression, and metastasis.[5] The tumor microenvironment is the cellular environment in which the tumor interacts with its microenvironment. Monocytes, which have an important role among the components of the tumor microenvironment, are the cells of the heterogeneous mononuclear phago-

Table 3. Disease-free survival analyses according to the monocyte count in patients with esophageal carcinoma

	Univariate		Multivariate	
	HR[a] (95% CI[b])	p-value	HR (95% CI)	p-value
Age (>60 vs ≤60)	1.366 (0.729-2.559)	0.331		
Sex (male vs female)	1.499 (0.803-2.800)	0.204		
Stage (M1 vs others)	4.648 (2.245-9.624)	<0.0001	2.844 (1.324-6.108)	0.007
Pathological Type (Adenocarcinoma vs SCC[c])	2.930 (1.410-6.087)	0.067	2.099 (0.900-4.897)	0.086
Monocyte count (µL) (<515/µL vs ≥515/µL)	3.348 (1.720-6.515)	<0.0001	2.702 (1.359-5.372)	0.005
Hemoglobin (g/dL) (<12g/dL vs ≥12g/dL)	0.910 (0.761-1.088)	0.797		
ECOG[d] (ECOG 0 vs ECOG1 - ECOG2)	2.114 (1.061-4.212)	0.033	2.133 (1.003-4.535)	0.049

[a]HR: Hazard Ratio; [b]CI: Confidence Interval; [c]SCC: Squamous Cell Carcinoma; [d]ECOG: The Eastern Cooperative Oncology Group.

cyte system that shows different responses to different stimuli rather than being a homogeneous cell population.[12] Monocytes differentiate into either M1 or M2 type macrophages depending on environmental signals. M1 macrophages have pro-inflammatory and anti-cancer functions, while M2 macrophages promote tumor growth. TAMs are generally similar to M2 macrophages. It is also known that TAMs contribute to pro-tumorigenic effects such as invasion, angiogenesis, and metastasis through the cytokines they secrete.[13] TAMs, which originate from monocytes, are key regulators of the tumor microenvironment and have been found to have an independent effect on the prognosis of various cancers.[14, 15] Although it is considered that soluble factors released from the tumor are effective in the development of TAMs, the exact mechanism of this occurrence remains unclear. TAMs are found extensively in numerous tumors, and the high number of TAMs infiltrating the tumor is also associated with the poor prognosis of the disease. Given that tissue inflammatory cells originate from blood and are controlled by common cytokines, it can be considered that peripheral blood cell count may reflect the severity of inflammation in the tumor microenvironment. Since monocytes are potential sources of TAMs, it is considered that monocyte count reflects the density of TAMs in the tumor microenvironment and may be a biomarker that can be used in daily practice. In addition, studies have shown that monocyte count is a reliable prognostic marker in both solid organ tumors and hematological tumors.[16, 17] Evani et al.[18] suggested that monocytes, unlike other inflammatory cells, promote tumor progression and have a role in metastasis. Moreover, some other studies showed that TAM infiltration in patients with esophageal cancer is generally associated with worse clinical outcomes and poor response to chemotherapy.[19, 20] In light of these findings and given the fact that monocyte count represents the formation or presence of TAMs, our study supports the studies that suggest that the monocyte count measured before treatment in patients with esophageal cancer is associated with disease progression and can be evaluated as an independent predictive marker of prognosis. Nonetheless, to the best of our knowledge, there is no standard cutoff value determined for monocyte count in the literature. Koh et al.[6] determined a cutoff value of 375/μL for the diagnosis of mantle cell lymphoma, which provided a sensitivity and specificity of 78% and 57%, respectively. The authors noted that patients with a monocyte count >375/μL had lower DFS. Han et al.[21] evaluated monocyte count in patients with esophageal cancer and performed the analysis by accepting the median monocyte count of the patients participating in the study as the cutoff value. The study was conducted in the Chinese population, which has a high prevalence of esophageal cancer and represents the yellow race. Accordingly, investigating the relationship between monocyte count and the prognosis of esophageal cancer in the Caucasian race, which is similar to the Turkish population and has a lower prevalence of esophageal cancer, is highly important. In our study, ROC curve analysis determined a cutoff value of 515/μL for monocyte count, which provided a sensitivity and specificity of 67.5% and 63.8%, respectively. Based on this cut-off value, a monocyte count ≥515/μL was associated with lower DFS.

Conclusion

Our findings indicated that the monocyte count assessed before treatment in patients with esophageal cancer is associated with disease progression and is an independent predictive marker of prognosis. In addition, the findings also showed that monocyte count, which indirectly shows TAM density in the tumor microenvironment, is effective on the prognosis. We consider that TAMs should be one of the future treatment targets and that the prognosis of tumors can be improved with the regulation of TAMs.

Our study was limited since it was a retrospective and single-center study and included a heterogeneous group that involved both esophageal adenocarcinoma and esophageal SCC patients. By contrast, the strength of the study lies in the analysis of the effect of monocyte count alone on DFS and prognosis, regardless of the histological subtypes of esophageal cancer. Further prospective and multicenter studies are needed to substantiate our findings.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and reviewed and approved by the Ethics Committee the University of Health Sciences, Van Training, and Research Hospital (2020/23).

Informed Consent Statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.O.K., U.C.; Design – N.O.K., U.C.; Supervision – N.O.K., U.C.; Materials – N.O.K., U.C.; Data collection and/or processing – N.O.K., U.C.; Literature search – N.O.K., U.C.; Writing – N.O.K.; Critical review – N.O.K., U.C.

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