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Prognostic Significance of Hematologic Markers in Patients with Head and Neck Squamous Cell Carcinomas

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Abstract

Aim: To assess the prognostic value of hematologic markers for cancers of the head and neck region, according to tumor site. **Methods:** We reviewed the data of 441 patients diagnosed with head and neck squamous cell carcinomas (HNSCC) between 2006 and 2014. Overall survival rates were estimated using the Kaplan-Meier method and Cox proportional hazards models were used to assess the hazard ratio (HR) for death, according to hematologic markers. **Results:** In the univariate analyses, hemoglobin concentration; leukocyte, neutrophil, monocyte, and platelet counts; and the platelet-lymphocyte ratio were associated with overall survival. In the multivariate analyses, hemoglobin concentration (HR 0.55, 95% confidence interval [CI] 0.38 - 0.78, $p < 0.001$) and leukocyte (HR 1.57, 95% CI 1.11 - 2.23, $p = 0.010$), monocyte (HR 1.86, 95% CI 1.25 - 2.73, $p = 0.003$), and platelet (HR 2.17, 95% CI 1.24 - 3.57, $p = 0.008$) counts were independent prognostic factors for HNSCC. None of the hematologic markers were significant prognosticators for oral cancer. Leukocyte (HR 2.67, 95% CI 1.17 - 6.58, $p = 0.018$), monocyte (HR 4.04, 95%CI 1.85 - 8.56, $p < 0.001$), and platelet (HR 3.77, 95% CI 1.55 - 8.28, $p = 0.005$) counts were independent prognostic factors for laryngeal cancer. **Conclusions:** Several hematologic markers have prognostic significance for patients with HNSCC, however, the magnitude of the effect depends on the tumor site.

Keywords

Biomarkers, Head and Neck Cancer, Hematologic Marker

1. Introduction

Various cancers arise in the head and neck region [1]; head and neck squamous cell carcinoma (HNSCC) is the most common. Treatment for HNSCC includes surgery, radiation therapy, chemotherapy, and immunotherapy. Generally, single modality treatment is selected for early stage HNSCC whereas multimodality treatment is selected for advanced stage HNSCC. Despite improved radiation techniques and the emergence of new drugs such as immune checkpoint inhibitors, advanced stage HNSCC still carries a poor prognosis. To improve the prognosis, biomarkers to detect early recurrence and to assist in decision-making regarding treatment selection and intensification, have been sought [2]. Most are either tumor tissue-derived or blood-derived. Human papilloma virus status, as determined by its surrogate marker (*i.e.*, p16) in tumor tissues, is the most important biomarker for HNSCC, and is required for TNM staging of oropharyngeal cancers [3]. Tissue biomarkers offer direct information on tumor cells and the surrounding environment, while blood biomarkers reflect indirect consequences of tumor development [2]. However, blood biomarkers offer an advantage in that repeated blood samples are easy to obtain.

A complete blood count (CBC) is routinely performed before, during, and after cancer treatment. The CBC roughly estimates the patient's anemic, inflammatory, immunologic, and nutritional status. Recently, the neutrophil, monocyte, and platelet counts; and the peripheral blood neutrophil-lymphocyte ratio (NLR); platelet-lymphocyte ratio (PLR); and lymphocyte-monocyte ratio (LMR)—all calculated from the CBC result—have been shown to be associated with prognosis in patients with solid tumors, including HNSCC [4] [5] [6] [7]. However, which marker should be used for prognostication in patients with HNSCC has not yet been elucidated. Meta-analyses of solid tumors have demonstrated that the magnitude of the prognostic effect of hematologic markers depends on the tumor site [5] [6] [7]. However, previous studies on HNSCC [4] [8] [9] [10], except for meta-analyses of NLR and PLR [11] [12], have not addressed differences in tumor site. This study aimed to determine the most reliable prognostic hematologic marker for HNSCC and to investigate the prognostic value of hematologic markers for tumors at various sites within the head and neck region.

2. Material and Methods

2.1. Patients and Data Extraction

A retrospective chart review was performed of all patients with newly diagnosed, histologically confirmed HNSCC who were treated at the Department of Otorhinolaryngology: Head and Neck Surgery, Osaka General Medical Center, between January 2006 and September 2014. The inclusion criteria were: 1) histologically or cytologically proven HNSCC, 2) HNSCC previously untreated, and 3) receiving curative-intent treatment. The exclusion criteria were: 1) the presence of distant metastases at initial diagnosis, 2) a follow-up period of less than 6

months, and 3) no available pretreatment data. A total of 573 patients with HNSCC were identified from our hospital's registry. Of these, 132 patients were excluded: 103 were treated with palliative intent, 7 had a short follow-up period, and 22 had no CBC data. The remaining 441 patients were included in this study. Their clinicopathologic characteristics (sex, age, primary site, TNM classification, and comorbidities at presentation), pretreatment hematologic marker results, outcomes, and follow-up period were analyzed. The severity of comorbidities was determined according to the Osaka Head and Neck Comorbidity Index [13].

2.2. Statistical Analysis

Patients were divided into 2 groups ("high" and "low") for each hematologic marker according to cut-off values determined by means of receiver operating characteristic curves. Survival was estimated using the Kaplan-Meier method and was compared using the log-rank test. A Cox proportional hazard model was used to obtain the hazard ratio for death. Each Cox model included a single hematologic parameter; we did not include ≥2 hematologic parameters simultaneously. Because of the limited number of patients, multivariate analyses were performed only for overall patients, patients with oral cancer, and patients with laryngeal cancer. A p-value <0.05 was considered to indicate statistical significance. JMP version 12 statistical software (SAS Japan, Tokyo, Japan) was used to perform all statistical analyses.

3. Results and Analysis

3.1. Patient Characteristics

The patients' clinicopathologic characteristics are shown in **Table 1**. The male-to-female ratio was 2.7:1, and the median age was 68 years (range, 27 - 92). The most common primary site was the oral cavity, followed by the larynx, oropharynx, hypopharynx, and other sites. In terms of staging, 34% of patients had advanced T-stage (3 or 4) and 25% had advanced N-stage (2 or 3) cancers. Comorbidity was categorized as being mild in 85% of the patients, moderate in 11%, and severe in 4%. The median follow-up period of surviving patients was 57.2 months (range 6.7 - 129).

Distribution of Hematologic Markers

The distribution of leukocyte, neutrophil, lymphocyte, monocyte, platelet, NLR, PLR, LMR is shown in **Figure 1**. In most patients, these markers were within normal limits, indicating that the hematologic markers are not useful for the diagnosis of head and neck cancer.

3.2. Association between Hematologic Parameters and Overall Survival

We divided the patients into 2 groups ("low" and "high") for each hematologic parameter and estimated the overall survival rates using the Kaplan-Meier me-

thod (Figure 2). The 5-year overall survival rates for patients in the low and high biomarker groups, respectively, were as follows: hemoglobin, 60.1% and 79.6% ($p < 0.001$; Figure 2(a)); leukocyte count, 77.6% and 59.9% ($p = 0.005$; Figure 2(b)); neutrophil count, 75.9% and 62.3% ($p = 0.021$; Figure 2(c)); lymphocyte count, 68.9% and 71.2% ($p = 0.832$; Figure 2(d)); monocyte count, 74.3% and 50.3% ($p < 0.001$; Figure 2(e)); platelet count, 71.4% and 48.3% ($p = 0.002$; Figure 2(f)); NLR, 75.4% and 69.3% ($p = 0.133$; Figure 2(g); PLR, 72.8% and 60.4% ($p = 0.030$; Figure 2(h)); and LMR, 64.9% and 74.6% ($p = 0.053$; Figure 2(i)).

Next, we investigated the hazard ratio (HR) of each hematologic marker for

Table 1. Patient characteristics.

	n = 441	
	No.	%
Sex		
male	324	73
female	117	27
Age, years		
median	68	
range	27 - 92	
Primary site		
oral cavity	195	44
larynx	122	28
oropharynx	43	10
hypopharynx	57	13
other	24	5
T		
T1, T2	290	66
T3, T4	151	34
N classification		
N0, N1	332	75
N2, N3	109	25
Stage		
I	140	32
II	79	18
III	67	15
IV	155	35
Comorbidity		
OHNCI = 0	377	85
1	47	11
≥2	17	4

Abbreviations: OHNCI, Osaka Head and Neck Comorbidity Index.

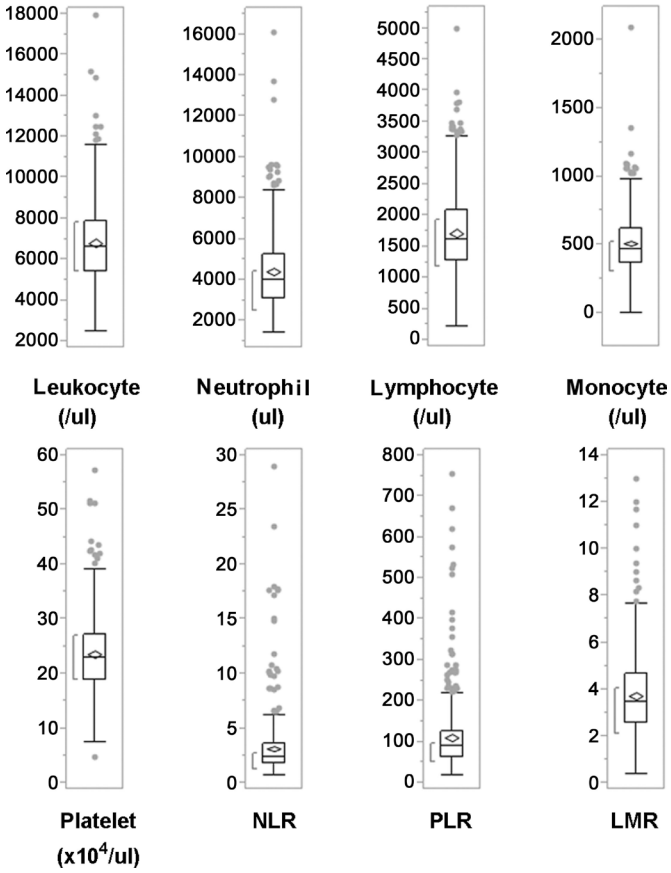

Figure 1. Distribution of hematologic markers.

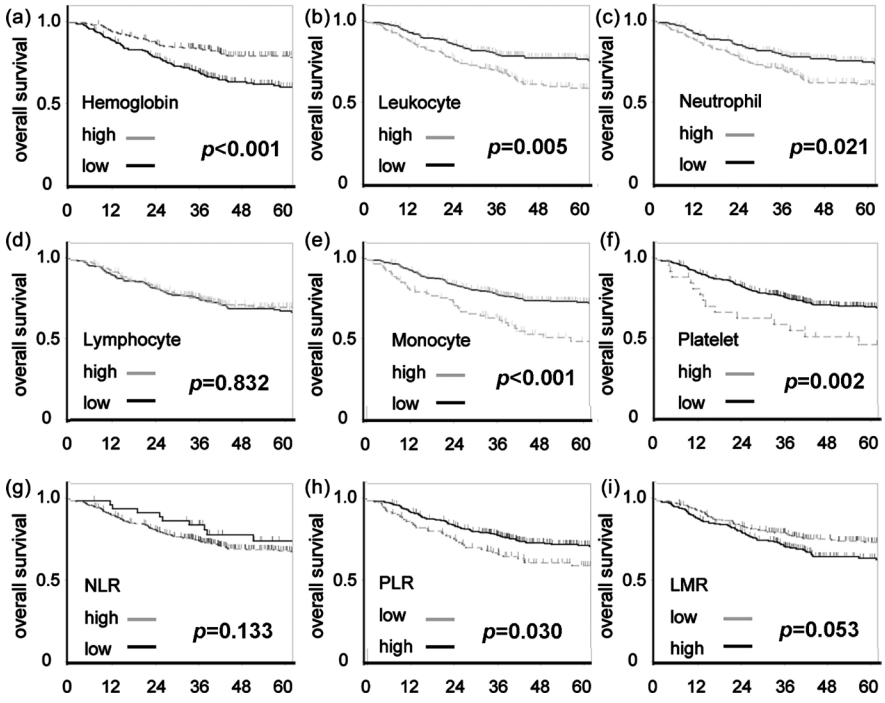

Figure 2. Overall survival by (a) hemoglobin level, (b) leukocyte count, (c) neutrophil count, (d) lymphocyte count, (e) monocyte count, (f) platelet count, (g) neutrophil lymphocyte ratio, (h) platelet-lymphocyte ratio, and (i) lymphocyte-monocyte ratio.

death, according to tumor site. Table 2(a) and Table 2(b) shows the result of the univariate analyses. In the analysis of oral and oropharyngeal cancers, none of the hematologic markers were associated with overall survival. On the other hand, the hemoglobin concentration (HR 0.47, 95% confidence interval [CI] 0.23 - 0.96, $p = 0.037$), leukocyte count (HR 2.14, 95% CI 1.04 - 4.73, $p = 0.039$), monocyte count (HR 3.25, 95% CI 1.54 - 6.59, $p = 0.003$), platelet count (HR 4.25, 95% CI 1.78 - 9.08, $p = 0.002$), and LMR (HR 0.40, 95% CI 0.19 - 0.81, $p = 0.011$) were significantly associated with the prognosis of patients with laryngeal cancer, and hemoglobin was associated with the prognosis of patients with hypopharyngeal cancer (HR 0.41, 95% CI 0.16 - 1.96, $p = 0.039$).

To exclude confounding, multivariate analyses were performed (Table 3). For the patients overall, each Cox proportional hazard models included a hematologic marker, T and N classification, age, comorbidity, and tumor site. Of the parameters, the hemoglobin concentration (HR 0.55, 95% CI 0.38 - 0.78, $p < 0.001$) and leukocyte (HR 1.57, 95% CI 1.11 - 2.23, $p = 0.010$), monocyte (HR

Table 2. The result of the univariate analysis among tumor site; (a) overall, oral cavity, and larynx, (b) oropharynx, hypopharynx, and other. The hazard ratio was adjusted for T, N and M classifications. HR, hazard ratio, CI, confidence interval, NLR, neutrophillymphocyte ratio, PLR, platelet-lymphocyte ratio, LMR, Lymphocyte-monocyte ratio, *$p < 0.05$.

(a)

	overall	(n = 441)	oral cavity	(n = 195)	larynx	(n = 122)
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
hemoglobin (g/dl)	0.51	<0.001*	0.61	0.064	0.47	0.037*
≥13.8 vs <13.8	(0.36 - 0.72)		(0.35 - 1.03)		(0.23 - 0.96)	
Leukocyte (/μl)	1.6	0.005*	1.43	0.185	2.14	0.039*
≥6800 vs <6800	(1.15 - 2.23)		(0.84 - 2.39)		(1.04 - 4.73)	
Neutrophil (/μl)	1.47	0.022*	1.28	0.358	1.41	0.337
≥4241 vs <4241	(1.06 - 2.05)		(0.75 - 2.13)		(0.70 - 2.89)	
Lymphocyte (/μl)	0.85	0.359	1.15	0.594	0.8	0.538
≥1776 vs <1776	(0.60 - 1.19)		(0.67 - 1.93)		(0.40 - 1.61)	
Monocyte (/μl)	1.94	<0.001*	1.59	0.205	3.25	0.003*
≥660 vs <660	(1.33 - 2.78)		(0.76 - 3.01)		(1.54 - 6.59)	
Platelet (103/μl)	2.23	0.005*	0.44	0.355	4.25	0.002*
≥345 vs <345	(1.29 - 3.59)		(0.03 - 2.01)		(1.78 - 9.08)	
NLR	1.67	0.109	1.17	0.785	1.64	0.383
≥1.30 vs 1.30	(0.90 - 3.53)		(0.43 - 4.81)		(0.58 - 6.86)	
PLR	1.49	0.036*	0.91	0.785	2.06	0.064
≥129 vs <129	(1.03 - 2.12)		(0.45 - 1.69)		(0.96 - 4.20)	
LMR	0.72	0.053	1.06	0.825	0.40	0.011*
≥3.46 vs <3.46	(0.52 - 1.00)		(0.64 - 1.78)		(0.19 - 0.81)	

(b)

	oropharynx	(n = 43)	hypopharynx	(n = 57)	other	(n = 24)
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
hemoglobin (g/dl)	0.38	0.079	0.41	0.039*	0.47	0.200
≥13.8 vs <13.8	(0.11 - 1.11)		(0.16 - 0.96)		(0.15 - 1.52)	
Leukocyte (/μl)	2.64	0.093	1.39	0.433	1.72	0.367
≥6800 vs <6800	(0.85 - 9.78)		(0.61 - 3.29)		(0.54 - 6.44)	
Neutrophil (/μl)	2.22	0.138	1.36	0.459	2.07	0.253
≥4241 vs <4241	(0.78 - 7.28)		(0.60 - 3.14)		(0.61 - 9.34)	
Lymphocyte (/μl)	0.82	0.721	0.74	0.513	0.80	0.732
≥1776 vs <1776	(0.26 - 2.47)		(0.27 - 1.78)		(0.18 - 2.69)	
Monocyte (/μl)	2.82	0.091	0.84	0.680	2.1	0.221
≥660 vs <660	(0.83 - 8.66)		(0.34 - 1.93)		(0.62 - 6.62)	
Platelet (103/μl)	5.49	0.204	2.14	0.205	2.41	0.229
≥345 vs <345	(0.28 - 37.57)		(0.62 - 5.76)		(0.53 - 8.33)	
NLR	2.24	0.385	1.59	0.505	N/A	N/A
≥1.30 vs 1.30	(0.44 - 40.82)		(0.47 - 9.95)		N/A	
PLR	1.94	0.221	1.18	0.712	2.09	0.211
≥129 vs <129	(0.65 - 5.32)		(0.47 - 2.72)		(0.65 - 6.74)	
LMR	0.56	0.273	1.07	0.881	1.32	0.630
≥3.46 vs <3.46	(0.19 - 1.59)		(0.39 - 2.62)		(0.41 - 4.24)	

1.86, 95% CI 1.25 - 2.73, $p = 0.003$), and platelet (HR 2.17, 95% CI 1.24 - 3.57, $p = 0.008$) counts were independent prognostic factors. For patients with oral or laryngeal cancers, each Cox proportional hazard model included a single hematologic marker, T and N classification, age, and comorbidity. None of the hematologic markers were significant prognosticators. The leukocyte (HR 2.67, 95% CI 1.17 - 6.58, $p = 0.018$), monocyte (HR 4.04, 95% CI 1.85 - 8.56, $p < 0.001$), and platelet (HR 3.77, 95% CI 1.55 - 8.28, $p = 0.005$) counts were independent prognostic factors for laryngeal cancer.

4. Discussion

Hematopoietic stem cells give rise to erythrocytes, platelets, neutrophils, lymphocytes, monocytes, and other cells. In the peripheral blood, these differentiated blood cells can easily be counted by visual inspection or via an automated analyzer. In patients with cancer, the number of these circulating blood cells falls outside the normal physiologic range. Malnutrition, commonly seen in cancer patients, leads to anemia [14]. Conversely, erythropoiesis may be enhanced as an adaptation to hypoxia [15]. Tumor cells also increase thrombocyte generation, resulting in paraneoplastic thromobocytosis [16]. Inflammation is a hallmark of cancer, and systemic inflammation caused by cancer changes the number of

Table 3. Multivariate analyses for overall survival.

	Overall*1	(n = 441)	Oral cavity*2	(n = 195)	Larynx*2	(n = 122)
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
hemoglobin (g/dl)	0.55	<0.001*	0.75	0.323	0.72	0.411
≥13.8 vs <13.8	(0.38 - 0.78)		(0.41 - 1.32)		(0.32 - 1.59)	
Leukocyte (/μl)	1.57	0.010*	1.32	0.328	2.67	0.018*
≥6800 vs <6800	(1.11 - 2.23)		(0.75 - 2.27)		(1.17 - 6.58)	
Neutrophil (/μl)	1.37	0.073	1.08	0.788	1.28	0.553
≥4241 vs <4241	(0.97 - 1.94)		(0.62 - 1.86)		(0.57 - 2.92)	
Lymphocyte (/μl)	0.95	0.767	1.31	0.332	1.08	0.839
≥1776 vs <1776	(0.67 - 1.34)		(0.76 - 2.22)		(0.51 - 2.30)	
Monocyte (/μl)	1.86	0.003*	1.56	0.237	4.04	<0.001*
≥660 vs <660	(1.25 - 2.73)		(0.73 - 3.03)		(1.85 - 8.56)	
Platelet (103/μl)	2.17	0.008*	0.43	0.337	3.77	0.005*
≥345 vs <345	(1.24 - 3.57)		(0.02 - 1.98)		(1.55 - 8.28)	
NLR	1.61	0.146	1.11	0.859	1.03	0.968
≥1.30 vs 1.30	(0.86 - 3.42)		(0.040 - 4.60)		(0.33 - 4.59)	
PLR	1.27	0.214	0.64	0.195	1.38	0.435
≥129 vs <129	(0.89 - 1.82)		(0.30 - 1.24)		(0.60 - 2.97)	
LMR	0.90	0.536	1.38	0.238	0.60	0.180
≥3.46 vs <3.46	(0.63 - 1.27)		(0.81 - 2.40)		(0.27 - 1.27)	

*[1]For overall patients, the hazard ratios were adjusted for T and N classifications, age, comorbidity and primary site. *[2]For patients with oral cancer or laryngeal cancer, the hazard ratios were adjusted for T and N classifications, age and comorbidity. HR, hazard ratio, CI, confidence interval, NLR, neutrophil-lymphocyte ratio, PLR, platelet-lymphocyte ratio, LMR, Lymphocyte-monocyte ratio, *$p < 0.05$.

circulating immune cells, such as neutrophils and lymphocytes [4]. Thus, the peripheral blood cell counts of cancer patients reflect tumor progression, and are, thus, potential prognostic markers. Recently, the number of reports published on the association between hematologic markers and cancer prognosis has rapidly increased [4]-[10] [17]. Although these hematologic markers can predict prognosis to some extent, each marker has a different prognostic capability.

In the present study, we investigated the prognostic impact of various hematologic markers for cancers at several head and neck sites. We found that hematologic markers did not predict the prognosis of patients with oral cancer, whereas monocyte and platelet counts had high prognostic capability for patients with laryngeal cancer.

One of the most extensively investigated hematologic markers is the NLR [8] [10] [11] [17] [18] [19]. The HRs of NLR ranged from 1.03 to 2.24 in the present study, comparable to results presented in a meta-analysis of head and neck cancers [11]. In the meta-analysis, the HR for overall survival was the lowest for oral

cancer and the highest for oropharyngeal cancer, consistent with the results of the present analysis. Another extensively investigated marker is the PLR [8] [10] [12] [18]. The HRs of PLR in the present study ranged from 0.64 to 2.06, while those in a meta-analysis of head and neck cancers ranged from 1.38 to 2.94 [12]. In the meta-analysis, PLR was a significant prognostic factor for patients with laryngeal cancer but not with oral cancer. In the present study, none of the hematologic markers showed any prognostic capability for oral cancer. Collectively, hematologic markers do not appear to be useful for oral cancer.

There were some limitations in this study. First, the number of patients, and thus the statistical power, differed for each cancer site. Second, because of the small number of patients with oropharyngeal and hypopharyngeal cancers, we were unable to perform a multivariate analysis for these cancers. Last, we determined cut-off values from and used these cut-off values in the same dataset. It is preferable that an independent dataset be used for the survival analyses.

5. Conclusion

We found that leukocyte, monocyte, and platelet counts were independent prognostic factors for overall survival in patients with laryngeal cancer, but that none of the hematologic markers assessed were prognostic factors for oral cancer. Further studies are required to assess the usefulness of hematologic markers in clinical practice.

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