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Prognostic Value of Lymphocyte-to-Monocyte Ratio for Japanese Patients With Differentiated Thyroid Cancer Treated With Sorafenib Therapy

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Abstract. *Background/Aim: We investigated the efficacy and safety of sorafenib in Japanese patients and the prognostic value of systemic immunity markers for predicting clinical outcomes after sorafenib therapy in patients with radioiodine refractory differentiated thyroid cancer (RR-DTC). Patients and Methods: We retrospectively evaluated 26 patients with RR-DTC who underwent sorafenib therapy between July 2014 and December 2020. The systemic immunity markers were calculated from blood cell counts. Results: The median overall survival (OS) was 2,002 days, and the clinical benefit rate was 80.8%. The high lymphocyte-to-monocyte ratio (LMR) group had significantly longer OS than the low LMR group (hazard ratio=0.21; 95% confidence interval=005-0.88; log-rank p=0.019). Adverse events observed in this study were acceptable, and no new safety signals associated with sorafenib were found. Conclusion: Sorafenib therapy is efficacious and safe for Japanese patients with RR-DTC, and baseline LMR may be useful as a sorafenib therapy prognostic marker.*

Although most patients with differentiated thyroid cancer (DTC) have a good prognosis, <10% of patients develop metastatic disease, mostly in the lungs and bones (1). The prognoses of these metastatic cases remain favorable if they maintain good response to radioiodine therapy (1). A retrospective study demonstrated that the 10-year overall survival (OS) after radioiodine therapy was 92% in patients who remained responsive to radioiodine therapy but only 19% in those who were radioiodine refractory (RR); the latter patients had poor OS (2). Other treatment modalities are required for patients with RR-DTC.

Recently, many new drugs have been developed for the treatment of RR-DTC. Sorafenib and lenvatinib, which are tyrosine kinase inhibitors (TKIs), have been approved by the Food and Drug Administration and the European Medicines Agency, and several guidelines recommend TKIs therapy for RR-DTC (1, 3, 4). Sorafenib is an oral kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, VEGFR-2, VEGFR-3, RET, Flt3, c-KIT, RAF (including BRAFV600E), and platelet-derived growth factor receptor β (5, 6). The DECISION study demonstrated that sorafenib therapy significantly improved progression-free survival (PFS) as compared with placebo in patients with RR-DTC and suggested it as a new treatment option for patients with RR-DTC. In addition, several retrospective studies also showed the efficacy of sorafenib therapy from real world experience (7-9).

However, both the efficacy of sorafenib therapy and its predictive markers in Japanese patients with RR-DTC in the real world remain uncertain. Systemic immunity markers such as absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been recently reported to be associated with clinical benefits and useful as prognostic markers for several cancers (10-13). Furthermore, the association between the systemic immunity markers and the efficacy of TKIs for RR-DTC has been reported (14-16). Therefore, we investigated the efficacy of sorafenib therapy in Japanese patients and the association between these markers and the survival benefits of sorafenib therapy to confirm the usefulness of systemic immunity markers as prognostic markers for patients with RR-DTC after sorafenib therapy.

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Key Words: Differentiated thyroid cancer, sorafenib, overall survival, prognostic marker, lymphocyte-to-monocyte ratio.

Patients and Methods

Patients and treatment. We reviewed the medical records of patients with RR-DTC who received sorafenib therapy between July 2014 and December 2020 at Fukuyama City Hospital, excluding patients who received sorafenib therapy for <1 month. The data cutoff was May 31, 2021.

The treatment dose and schedule were based on those indicated in the DECISION study (6). The starting sorafenib dose was 400 mg twice a day. Dose interruption, reduction, or re-escalation was allowed on the physician's judgment or the patient's preference. The treatment was continued until progression, unacceptable toxicity, or patient/physician decision. Tumor response to sorafenib therapy was assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (17). We assessed the incidence of adverse events (AEs) according to the Common Terminology Criteria for Adverse Events v5.0 (18).

This retrospective study was approved by the review board of Fukuyama City Hospital (approval No. 567). All the procedures that involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants in the form of an opt-out on the website included in the study.

Measurements of systemic immunity markers. The measurement methods for the systemic immunity markers were the same as those used in our previous study and were previously described (19). In brief, ALC, NLR, PLR, and LMR were calculated from blood cell counts and evaluated at the start of sorafenib therapy. We defined the cutoff values of these markers on the basis of those reported in previous studies as follows: 1,500/μl for ALC, 3 for NLR, 150 for PLR, and 4 for LMR (11-16, 19). We divided the patients into the low and high groups according to the cutoff values.

Statistical analyses. We compared the continuous variables using the Wilcoxon rank sum test and the proportions of categorical variables using the Fisher exact test between the groups. The time to treatment failure (TTF) and OS were estimated with the Kaplan–Meier method and compared with the log-rank test. We performed a univariate Cox regression analysis to determine the association of the baseline patient characteristics with TTF and OS. We did not conduct a multivariate Cox regression analysis because of the small sample size. We considered a p-value <0.05 as statistically significant. We performed all statistical analyses using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (20).

We used the same definitions as those in our previous study (19). We defined TTF as the time from the administration of sorafenib to the discontinuation of treatment for any reason, including disease progression, treatment toxicity, patient/physician decision, and death from any cause. OS was defined as the time from the administration of sorafenib to the date of death from any cause. Overall response rate (ORR) was defined as the percentage of patients who achieved a complete or partial response according to the RECIST criteria (17). Clinical benefit rate (CBR) was defined as the percentage of patients who achieved a complete response, partial response, or stable disease (>6 months) according to the RECIST criteria (17).

Table I. *Patients' characteristics at the time of sorafenib treatment initiation*.

Variable	Total n=26 (%)
Age, years	74 (53-86)
Gender	
Male	10 (38.5)
Female	16 (61.5)
ECOG PS	
0	18 (69.2)
1	7 (26.9)
2	1 (3.8)
Diagnosis	
Locally advanced	6 (23.1)
Recurrence	20 (76.9)
Histology	
Papillary	21 (80.8)
Follicular	4 (15.4)
Poorly differentiated	1 (3.8)
Metastatic sites, n (%)	
Bone	11 (42.3)
Lungs	23 (88.5)
Lymph nodes	17 (65.4)
Subjective symptoms	11 (42.3)
Anti-thyroglobulin antibody	7 (26.9)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Results

Patients. We identified 32 patients with RR-DTC who received sorafenib therapy between July 2014 and December 2020 at Fukuyama City Hospital and excluded 6 patients who received sorafenib therapy for <1 month. Finally, we included 26 patients with RR-DTC in this study. The patients' characteristics are shown in Table I. The median age at sorafenib administration was 74 years (range=53-86 years). Of the patients, 16 (61.5%) were female, 21 (80.8%) were diagnosed as having papillary carcinoma, and 23 (88.5%) had lung metastases. The median values of the systemic immunity markers were as follows: ALC, NLR, PLR, and LMR were 1,481/μl, 2.06, 133.3, and 5.37, respectively.

Efficacy of sorafenib therapy. The median follow-up time was 969 days. The median TTF was 543 days [95% confidence interval (CI)=355-1882], and the median OS was 2,002 days (95%CI=985-not reached; Figure 1A and B). The ORR and CBR were 11.5% and 80.8%, respectively. Sorafenib therapy was discontinued because of disease progression in 11 patients (42.3%), AEs in 4 patients (15.4%), and other reasons in 3 patients (11.5%). Eight patients (30.8%) were still receiving sorafenib therapy at the time of data cutoff.

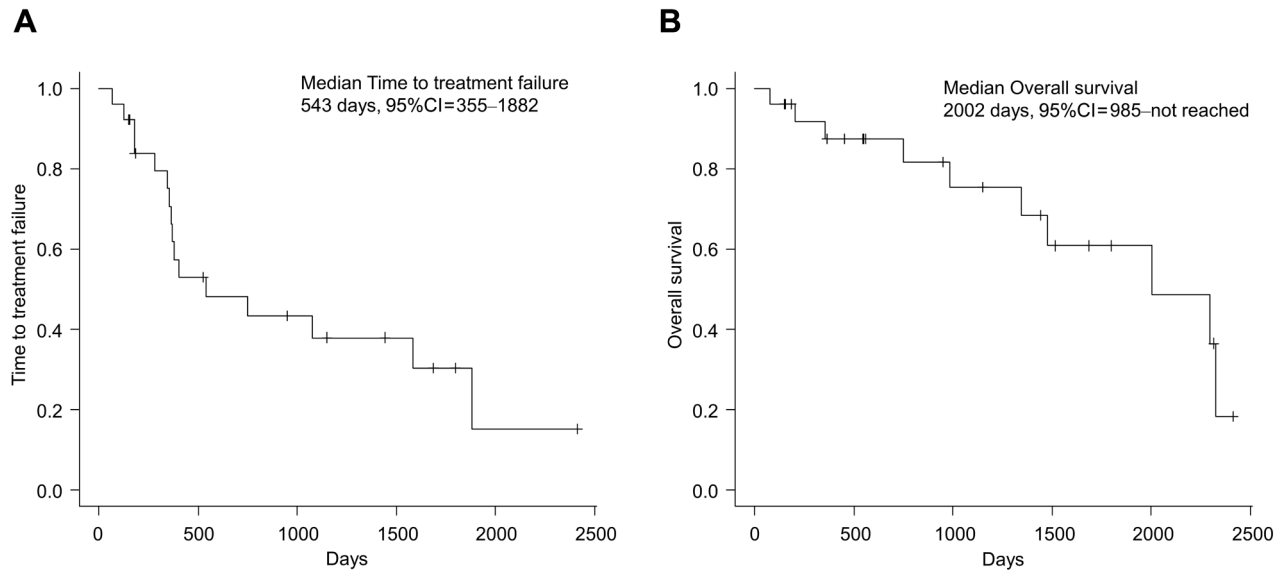

Figure 1. *Time to treatment failure (A) and overall survival (B) in the patients treated with sorafenib therapy.*

Impact of the systemic immunity markers on survival benefit. We compared the TTF according to the systemic immunity markers (Figure 2). We found no significant differences in TTF between the groups with high and low values of the systemic immunity markers. We performed a univariate analysis to determine the efficacy of sorafenib therapy in terms of survival benefit, including the systemic immunity markers (Table II). The univariate analysis revealed no significant association between TTF and the characteristics of patients. The systemic immunity markers had no impact on TTF.

We also compared OS according to the systemic immunity markers (Figure 3). The median OS of the high LMR group was significantly longer than that of the low LMR group [2,327 days (95%CI=985-not reached) *vs*. 1,346 days (95%CI=77-not reached; hazard ratio (HR)=0.21; 95%CI=0.05-0.88; log-rank p=0.019)]. The other 3 systemic immunity markers had no impact on OS (Table II).

Safety. In this study, all the patients experienced AEs (Table III); however, these AEs were mainly judged as grade 1 or 2. The common AEs (all grade) included hand-foot skin reaction (92.3%), hypertension (65.4%), alopecia (38.5%), rash or desquamation (34.6%), and anorexia (30.8%). The following serious AEs also occurred: interstitial pneumonitis (1 patient, 3.8%) and keratoacanthoma (1 patient, 3.8%).

Discussion

To the best of our knowledge, this is the first study to show the efficacy and safety of sorafenib therapy in Japanese patients with RR-DTC. Our findings are consistent with the results of previous studies in other countries (6-9). In addition, our findings indicated an association between high LMR and longer OS.

The efficacy of sorafenib therapy has been reported (6-9). The DECISION study demonstrated that the median PFS was significantly longer in the sorafenib group than in the placebo group (10.8 *vs*. 5.8 months; HR=0.59; 95%CI=0.45-0.76; p<0.001) and improved PFS was consistently observed in the prespecified subgroups, irrespective of mutation status (6). A multicenter retrospective cohort study showed that the median PFS was 9.7 months in Korean patients with RR-DTC who received sorafenib therapy, which is consistent with the findings of the DECISION study (7). A prospective single-center study showed that the median PFS and OS were 17.6 and 28.9 months, respectively, in Chinese patients with RR-DTC who received sorafenib therapy (8). A retrospective study showed that the median PFS was 17.3 months in Taiwanese patients with RR-DTC who received sorafenib therapy (9). In this study, the median TTF and OS were 543 and 2002 days, respectively, in the Japanese patients with RR-DTC who received sorafenib therapy. These findings showed a longer TTF than the results of the DECISION study (6) and were consistent with the findings of previous real-world studies (7-9). Our results also showed that the safety profile of sorafenib was similar to that observed in previous studies (7-9), and no new safety signals associated with the therapy were found. Given these findings, sorafenib therapy is also an effective treatment option for Japanese patients with RR-DTC (6-9).

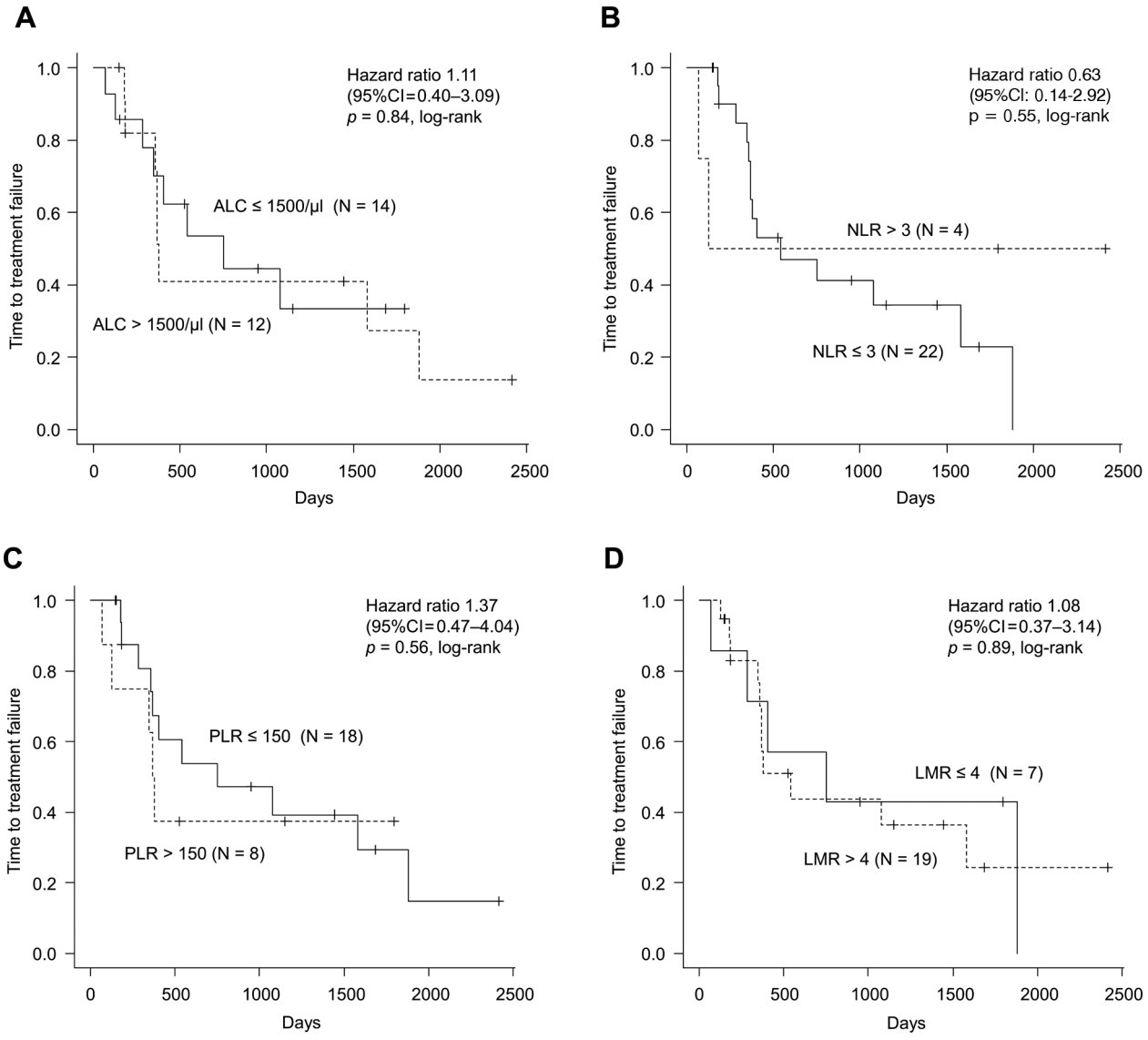

Figure 2. *Time to treatment failure according to baseline (A) ALC, (B) NLR, (C) PLR, and (D) LMR in patients who received sorafenib therapy. ALC: Absolute lymphocyte count; CI: confidence interval; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.*

Recently, the association between the systemic immunity markers and survival benefit and the usefulness of these markers as prognostic markers have been reported in various carcinomas (10-13). Furthermore, the usefulness of the markers as predictive markers of the effectiveness of certain treatments has also been reported in advanced breast cancer (19, 21, 22). In RR-DTC, the association between the NLR and the efficacy of lenvatinib therapy has been reported (14, 15). A retrospective analysis of data from the SELECT study showed that the baseline low NLR group had improved PFS (HR=0.43; 95%CI=0.29-0.65; p<0.001) and OS (HR=0.48; 95%CI=0.29-0.78; p=0.003) as compared with the baseline high NLR group (15). A meta-analysis evaluated the prognostic value of LMR for predicting the clinical outcomes in non-hematologic solid tumors and reported that low LMR was significantly associated with poor OS (HR=1.73; 95%CI=1.55-1.93; p<0.001) (13). A retrospective study showed that low LMR was associated with poor survival and was an independent risk factor of mortality in patients with anaplastic thyroid carcinoma (HR=2.55; 95%CI=1.08-6.00; p=0.032) (23). Furthermore, a retrospective cohort study reported that low LMR was associated with poor OS in

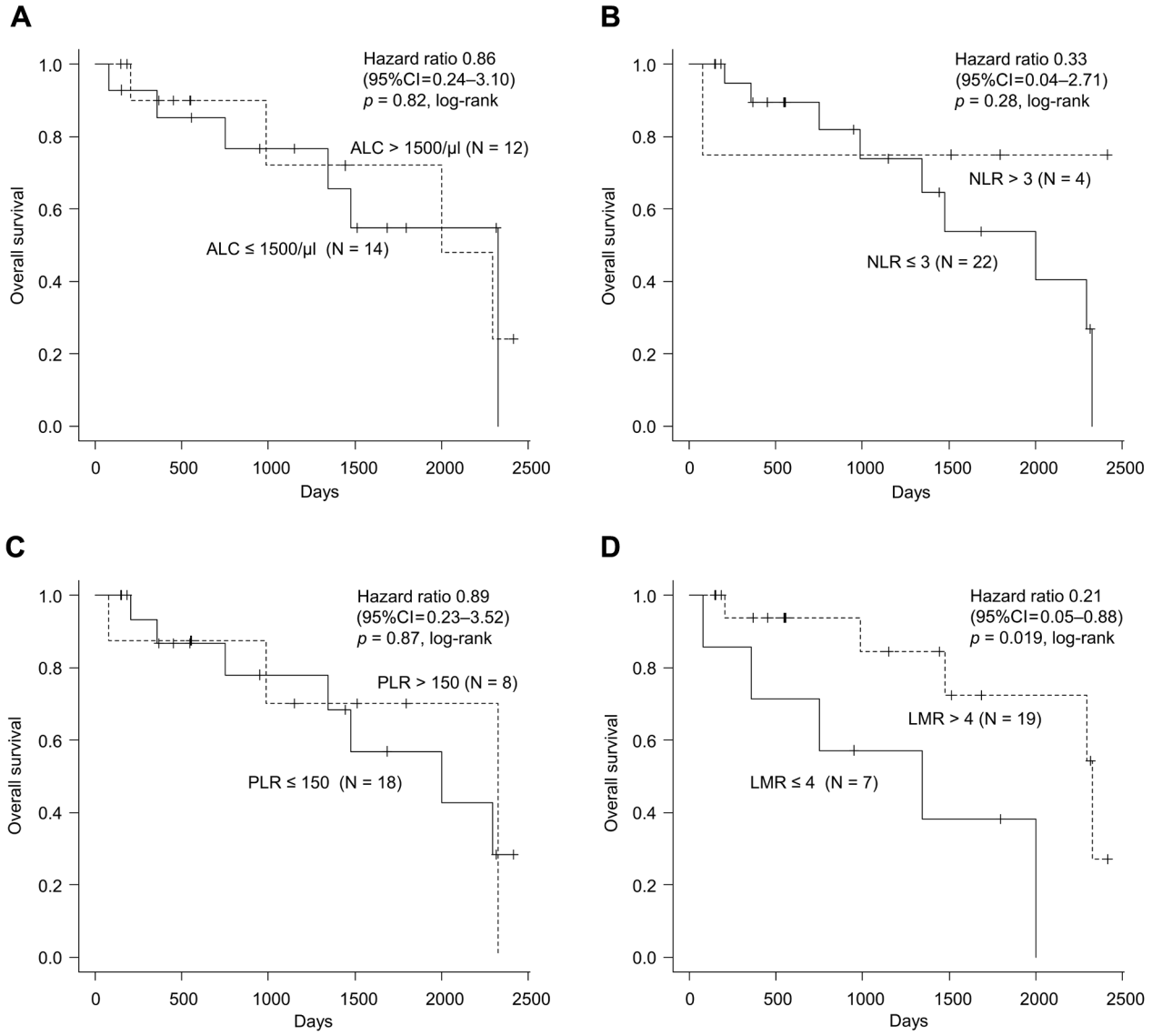

Figure 3. *Overall survival according to baseline (A) ALC, (B) NLR, (C) PLR, and (D) LMR in patients who received sorafenib therapy. Abbreviations: ALC: Absolute lymphocyte count; CI: confidence interval; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.*

Korean patients with progressive RR-DTC who received sorafenib therapy (16). Therefore, we evaluated the association between these markers and the survival benefits for sorafenib. Our results indicated that the high LMR group had significantly longer OS than the low LMR group. Tumor-associated macrophages (TAMs) derive from circulating monocytes and synthesize and release growth factors and cytokines that promote angiogenesis, anti-immune responses, and tumor progression (13, 23, 24). Peripheral blood absolute monocyte count may be a surrogate biomarker of TAMs, and LMR is calculated from the peripheral blood monocyte count, which may reflect the microenvironment for the tumor (13, 23). Given these findings, it is reasonable to consider LMR as a prognostic marker for predicting the clinical outcomes after sorafenib therapy in Japanese patients with RR-DTC.

Our study has several limitations. First, this study consisted of a small sample and unintentional selection bias is possible because of its nature as a retrospective single-center study. Given that we could not perform a multivariate analysis because of the small sample size, the results should be interpreted with caution. Second, the optimal cutoff

Table II. *Univariate analysis of time to treatment failure and overall survival (Cox hazard model).*

Variable	TTF			OS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age	1.08	1.00-1.17	0.065	1.05	0.95-1.15	0.33
Gender (male *vs*. female)	0.87	0.32-2.41	0.79	3.59	0.84-15.4	0.086
Diagnosis (recurrence *vs*. locally advanced)	1.02	0.28-3.63	0.98	1.13	0.13-9.72	0.91
Metastatic site (yes *vs*. no)						
Bone	1.05	0.38-2.92	0.92	1.62	0.43-6.06	0.47
Lungs	1.20	0.27-5.35	0.81	0.47	0.09-2.46	0.37
Lymph nodes	2.18	0.61-7.79	0.23	5.04	0.61-41.6	0.13
Subjective symptoms (yes *vs*. no)	1.08	0.40-2.89	0.88	1.06	0.82-1.36	0.68
Disease-free interval (<24 months *vs*. ≥24)	1.43	0.50-4.05	0.50	0.85	0.24-3.07	0.81
Anti-thyroglobulin antibody (yes *vs*. no)	0.75	0.24-2.38	0.62	0.35	0.04-2.80	0.32
Marker of systemic immunity at baseline						
ALC >1,500/μl *vs*. ALC ≤1,500/μl	1.11	0.40-3.09	0.84	0.86	0.24-3.10	0.82
NLR >3 *vs*. NLR ≤3	0.63	0.14-2.92	0.55	0.33	0.04-2.71	0.30
PLR >150 *vs*. PLR ≤150	1.37	0.47-4.04	0.57	0.89	0.23-3.52	0.87
LMR >4 *vs*. LMR ≤4	1.08	0.37-3.14	0.89	0.21	0.05-0.88	**0.033**

ALC: Absolute lymphocyte count; CI: confidence interval; HR: hazard ratio; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PLR: platelet-to-lymphocyte ratio; TTF: time to treatment failure. Value in bold indicates statistical significance.

values of the systemic immunity markers remain uncertain, and we used the cutoff values from previous studies (11-16, 19). Third, the most optimal prognostic marker among ALC, NLR, PLR, and LMR is uncertain, although our results suggest LMR as optimal. Therefore, our results should be confirmed by further prospective studies or studies consisting of a larger sample.

In conclusion, this study showed the efficacy and safety of sorafenib therapy in Japanese patients and the association between the systemic markers and survival benefit of sorafenib therapy. LMR may be a prognostic marker for patients with RR-DTC after receiving sorafenib therapy.

Conflicts of Interest

Shogo Nakamoto has received lecture fees from Chugai Pharmaceuticals, Eisai, and Taiho Pharmaceuticals. Masahiko Ikeda has received lecture fees from Beyer, AstraZeneca, Chugai Pharmaceuticals, Daiichi-Sankyo, Eisai, Eli-Lilly, Kyowa Kirin, Pfizer, Nippon Kayaku, Novartis, Mundipharma, Celltrion Healthcare Japan, and Sawai Pharmaceuticals outside the submitted work. The other Authors have no conflicts of interest to declare.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation and data collection were performed, and the first draft of the manuscript was written by Shogo Nakamoto. All Authors commented on the previous versions of the manuscript and read and approved the final version.

Table III. *Adverse events.*

	Any grade, n (%)	Grade 3/4, n (%)
Hand-foot skin reaction	24 (92.3)	9 (34.6)
Digestive symptoms*	3 (11.5)	0
Alopecia	10 (38.5)	0
Rash or desquamation	9 (34.6)	0
Fatigue	5 (19.2)	0
Hypertension	17 (65.4)	11 (42.3)
Anorexia	8 (30.8)	0
Oral mucositis	6 (23.1)	0
Paronychia	2 (7.7)	0
Interstitial pneumonia	1 (3.8)	1 (3.8)
Increased aspartate aminotransferase level	3 (11.5)	1 (3.8)
Increased alanine aminotransferase level	3 (11.5)	2 (7.7)

*Included nausea, diarrhea, and constipation.

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