Dynamic changes in practical inflammation and immunity markers in cancer patients receiving immune-enhancing nutritional supplementation during concurrent chemoradiotherapy

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Abstract.
BACKGROUND: Immune-enhancing nutrition (IMN) strengthens the systematic inflammatory response and the immune system. Neutrophil to lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) are affected during cancer therapies.
OBJECTIVE: We carried out an analysis of the dynamic changes in NLR and ALC over time in cancer patients with or without IMN supplementation.
METHODS: 88 cancer patients receiving concurrent chemoradiotherapy (CCRT) were randomized into regular diet group, and regular diet and IMN group.Generalized estimation equation models were used to assess associations between patient's characteristics, IMN, and dynamic changes in NLR and ALC over time.
RESULTS: NLR and ALC at pre-CCRT were significantly associated with dynamic changes in NLR (adjusted $\beta = 1.08$, 95% confidence interval [CI]: 0.64–1.52) and ALC (adjusted $\beta = 0.41$, 95% CI: 0.36–0.46). The magnitudes of the NLR and ALC changes through CCRT were lower in patients receiving IMN, although the differences were not statistically significant except ALC at the end of CCRT in head and neck cancer patients ($P = 0.023$).
CONCLUSION: Dynamic negative changes in both markers were demonstrated throughout CCRT. There were non-significant trend in promising changes in both NLR and ALC values in the whole group in IMN supplementation.

Keywords: Concurrent chemoradiotherapy, immune-enhancing nutrition, neutrophil to lymphocyte ratio, absolute lymphocyte count, cancer

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1. Introduction

The majority of patients receiving concurrent chemoradiotherapy (CCRT) have poor nutritional statuses [1–3] associated with deteriorated lymphoid tissue and subsequent weakening of the immune function [4]. In addition to the disease factor, CCRT itself also induces inflammation and immunological suppression that may cause other treatment-related toxicities [1–3].

The sufficiency of energy and protein intake is an important nutritional management option for patients receiving CCRT [2,3]. Nutritional supplementation improves several nutritional markers, such as albumin and prealbumin levels, lymphocyte count, etc. [5].

Immune-enhancing nutrition contains specific supplements that can moderate the inflammatory and immune responses [3,6,7]. Immune-enhancing nutritional supplementation is thought to strengthen the systematic inflammatory response and the immune system, which are known to be involved in the treatment response, progression, and prognosis in cancer patients [2,3,8,9]. A study on immune-enhancing nutrition has shown that dietary arginine, glutamine, and omega-3 fatty acid supplementation in immunocompromised patients (including cancer patients) improved immunity and decreased inflammation markers [10].

Although the inflammation response and immunity can be measured via many laboratory tests, the most sophisticated ones are not widely available in real-life practice. Complete blood count (CBC), a routine laboratory test accessible to most hospitals, can be used to evaluate inflammation and immunity [11]. The neutrophil to lymphocyte ratio (NLR; the percentage of neutrophils divided by the percentage of lymphocytes from a CBC test) is an inflammation-based score that is used as a predictor for the prognosis and survival of cancer patients. An increase in NLR is associated with poor prognosis and lower survival of head and neck, esophageal, and cervical cancers [12–16], and unfavorable outcomes in various other cancers [17]. In addition, NLR is associated with the nutritional status: a higher NLR is found in patients who are malnourished compared with those with a normal nutritional status [18].

Lymphocytes have an essential function in the cancer-related immune response, and the absolute lymphocyte count (ALC; the number of lymphocytes circulating in peripheral blood) is a prognostic factor for clinical outcomes of cancer patients [19–21]. Lymphopenia, a condition in which lymphocytes decrease to less than the normal value, is considered as a sign of immunosuppression [22] and is an independent predictor of chemotherapy-associated toxicity as well as mortality [23–28]. Both radiotherapy and chemotherapy can negatively impact lymphocyte count [29–31]. In addition, patients with low ALC have a worse response to therapy and shorter progression-free survival [32–35].

In our previous study, nutrition counseling combined with immune-enhancing nutritional supplementation agents (arginine, glutamine, and fish oil) reduced the deterioration of nutritional status and also the severity of CCRT toxicity [8]. However, the relationship between immune-enhancing nutritional supplementation and practical inflammation and immunity markers NLR and ALC has rarely been studied in cancer patients undergoing CCRT. In this study, we carried out an analysis of the dynamic changes in NLR and ALC over time to evaluate the impact of immune-enhancing nutritional supplementation agents on cancer patients undergoing CCRT.

2. Materials and methods

2.1. Patients

We obtained data from our prospective analysis of patients enrolled in a multicenter, randomized control study conducting between December 2013 and February 2015 among three cancer centers: Chiang Mai University Hospital, Prince Songklanagarind University Hospital, and Maharat Nakhonratchasima Hospital [9]. Eighty-eight cancer patients who received definitive CCRT, including 40 head and neck cancer patients, 28 esophageal cancer patients, and 20 cervical cancer patients were included in the study. Head and neck cancer patients received 60–70 Gy concurrent with weekly cisplatin 40 mg/m^2 or weekly carboplatin AUC 2, 50.4 Gy. Esophageal cancer patients received 50.4 Gy concurrent with 75 mg/m^2 of cisplatin on day 1 and 1,000 mg/m^2 of fluorouracil on day 1–4 every 28 days. Cervical cancer patients received 56 Gy concurrent with weekly 40 mg/m^2 of cisplatin or weekly carboplatin AUC 2 plus brachytherapy 28 Gy in 4 fractions. Patients were randomly assigned to two groups: group A (control arm) receiving a regular diet with energy 1,500 kcal and 60 g of protein per day, except esophageal cancer patients receiving blenderized nutrition with 2000 kcal and 75 g of protein per day via feeding tube, and group B (study arm) receiving a regular diet with additional 500 kcal per day of immune-enhancing nutritional supplementation containing arginine 6.16 g, L-glutamine 3.07 g, and fish oil 2.73 g that prepared in sachet form and provided 2 times per day during CCRT.

Table 1
Median and interquartile range of the neutrophil to lymphocyte ratio and absolute lymphocyte count before and during CCRT

	n	NLR			ALC		
		Median	IQR	P	Median	IQR	P
All cancer sites [$n = 88$]				< 0.001			< 0.001
Pre-CCRT	88	2.26	1.62 to 3.54		2,070	1,723 to 2,420	
Mid-CCRT	87	6.54	4.41 to 10.35		616	414 to 910	
End-CCRT	86	7.90	5.82 to 15.04		377	234 to 525	
Head and neck cancer [$n = 40$]				< 0.001			< 0.001
Pre-CCRT	40	2.08	1.58 to 2.93		2,042	1,723 to 2,835	
Mid-CCRT	40	7.76	6.00 to 10.56		685	530 to 890	
End-CCRT	40	7.58	4.63 to 12.87		421	281 to 561	
Esophageal cancer [$n = 28$]				< 0.001			< 0.001
Pre-CCRT	28	2.19	1.73 to 3.84		2,101	1,786 to 2,542	
Mid-CCRT	27	5.36	3.32 to 8.10		526	229 to 926	
End-CCRT	26	12.19	6.00 to 22.75		255	140 to 538	
Cervical cancer [$n = 20$]				< 0.001			< 0.001
Pre-CCRT	20	2.75	1.89 to 4.25		2,123	1,261 to 2,634	
Mid-CCRT	20	6.42	4.55 to 10.72		560	360 to 1,064	
End-CCRT	20	7.20	6.16 to 11.85		377	315 to 489	

Abbreviations: ALC, absolute lymphocyte count; CCRT, concurrent chemoradiotherapy; IQR, interquartile range; NLR, neutrophil to lymphocyte ratio; P, P-value from Friedman test to compare NLR and ALC between pre-CCRT, mid-CCRT, and end-CCRT.

2.2. Ethics approval and consent to participate

All subjects provided the institutional approved informed consents. This study was approved by each institutional ethics committee (i.e., Chiang Mai University Hospital, Prince Songklanagarind University Hospital and Maharaj Nakhonratchasima Hospital).

2.3. NLR and ALC measurements

NLR was calculated at each treatment visit (pre-CCRT, mid-CCRT, and end-CCRT) by dividing the percentage of neutrophils by the percentage of lymphocytes.

ALC was calculated as white blood cell count $\times$ 1,000 $\times$ the percentage of lymphocytes at pre-CCRT, mid-CCRT, and end-CCRT.

NLR and ALC percent changes from pre-CCRT to mid-CCRT or end-CCRT: NLR or ALC %change = (mid-CCRT or end-CCT value – pre-CCRT value/pre-CCRT value) $\times$ 100.

2.4. Statistical analysis

Patient characteristics at pre-CCRT were compared between the two groups (group A and group B) using the Chi-square or Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. Median NLR and ALC were compared between the two groups (group A and group B) using the Mann-Whitney test. NLR and ALC between the three treatment vis-

its (i.e., pre-CCRT, mid-CCRT, and end-CCRT) were compared using the Friedman test. Percent changes of NLR and ALC from pre-CCRT to mid-CCRT and end-CCRT were compared between the two groups (group A and group B) using the Mann-Whitney test. Univariable and multivariable generalized estimation equation (GEE) models were used to assess the association between dynamic changes of NLR and ALC over time and the following characteristics: gender, cancer site (i.e., head and neck, esophageal, or cervical cancer), age, body mass index (BMI) at pre-CCRT, and study group (group A and group B). Clinically relevant variables or covariates from univariable analyses with $P < 0.100$ were included in the multivariable models; covariates found to be collinear were excluded from the multivariable model. With the inclusion of the study groups and cancer sites being forced into the model, a backward model selection procedure was used to identify the multivariable model with the best overall fit.

3. Results

Patient characteristics at pre-CCRT, including age, gender, weight, height, body mass index, albumin, hemoglobin, tumor sites, tumor grade, tumor stage and Eastern Cooperative Oncology Group (ECOG) performance status were compared between groups A and B, as reported in Supplementary Table S1. There were no significant differences in characteristics at pre-CCRT between the two groups ($P > 0.05$).
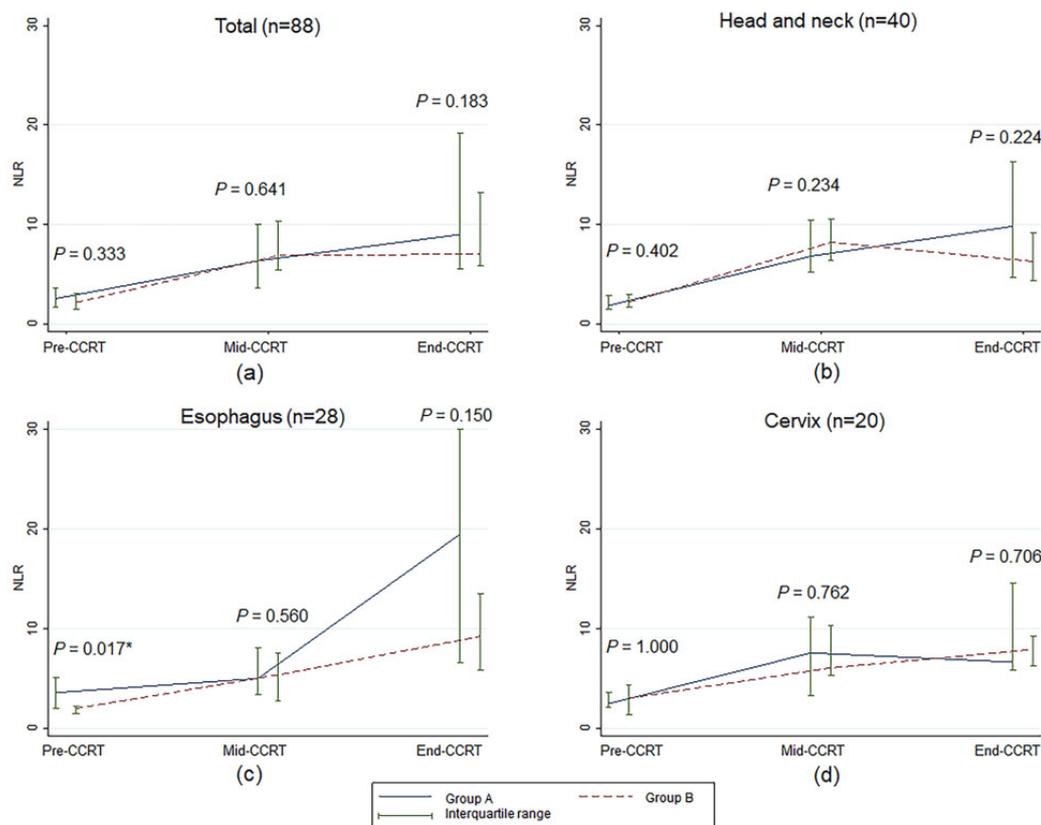
Fig. 1. Median and interquartile range of the neutrophil to lymphocyte ratio over time according to treatment visit for concurrent chemoradiotherapy. NLR, neutrophil to lymphocyte ratio; P, P-value from the Mann-Whitney test to compare NLR between two groups at each treatment visit; *$P <$ 0.05.

Table 1 reports the medians for NLR and ALC at pre-CCRT compared with mid-CCRT and end-CCRT for all patients and each cancer site. Overall, median NLRs at mid-CCRT and end-CCRT were higher than those at pre-CCRT (6.54 at mid-CCRT and 7.90 at end-CCRT compared to 2.26 at pre-CCRT; $P < 0.001$). Meanwhile, ALCs at mid-CCRT and end-CCRT were significantly lower than the pre-CCRT level for all patients and each cancer site ($P < 0.001$).

As shown in Fig. 1, NLRs at pre-CCRT, mid-CCRT, and end-CCRT were not significantly different between groups A and B for all cancer sites, except that the median NLR value of esophageal cancer patients at pre-CCRT in group A was higher than in group B. However, the difference between the two groups was not statistically significant throughout the CCRT course (Fig. 1c). There were no statistically significant differences in the median ALCs between the two groups for overall patients, esophageal cancer patients, and cervical cancer patients (Fig. 2). For the head and neck cancer patients,

ALC at end-CCRT was higher in group B compared with group A ($P = 0.023$), as shown in Fig. 2b.

In Table 2, it can be seen that NLR increased throughout CCRT compared to pre-CCRT in both groups. The NLR value of patients in group B increased less, although the change was not statistically significant. ALC decreased during CCRT compared to pre-CCRT in the two groups; the decrease in patients in group B was less, although the change was not statistically significant.

A GEE model was used to identify factors associated with NLR and ALC changes over time in Table 3. At the multivariate level, NLR at pre-CCRT was independently associated with an increase in NLR over time. NLR during CCRT increased by 1.08 (95% confidence interval [95% CI]: 0.64–1.52) for each unit increase in pre-CCRT NLR in which a higher NLR level at pre-CCRT was significantly associated with a higher NLR after CCRT ($P < 0.001$).

After adjusting for the study groups, NLR at pre-CCRT, and cancer sites, we found that NLR at mid-CCRT increased 5.33 times compared to pre-CCRT,

Table 2
Percentage changes in the neutrophil to lymphocyte ratio and absolute lymphocyte count from pre-CCRT to mid-CCRT and end-CCRT ($n = 88$)

Variables	Group A		Group B		P
	Median	Interquartile range	Median	Interquartile range	
NLR					
Pre-CCRT to mid-CCRT	59.03	39.20 to 74.65	66.68	38.11 to 81.55	0.443
Pre-CCRT to end-CCRT	75.51	37.75 to 85.78	69.79	59.46 to 79.17	0.458
ALC					
Pre-CCRT to midCCRT	−243.71	−411.84 to −113.39	−262.26	−407.73 to −144.13	0.502
Pre-CCRT to end-CCRT	−503.65	−934.08 to −317.40	−413.10	−620.61 to −198.90	0.190

Abbreviations: ALC, absolute lymphocyte count; CCRT, concurrent chemoradiotherapy; NLR, neutrophiltolymphocyte ratio; P, P-value from the Mann-Whitney testto compare NLR and ALC between two groups.
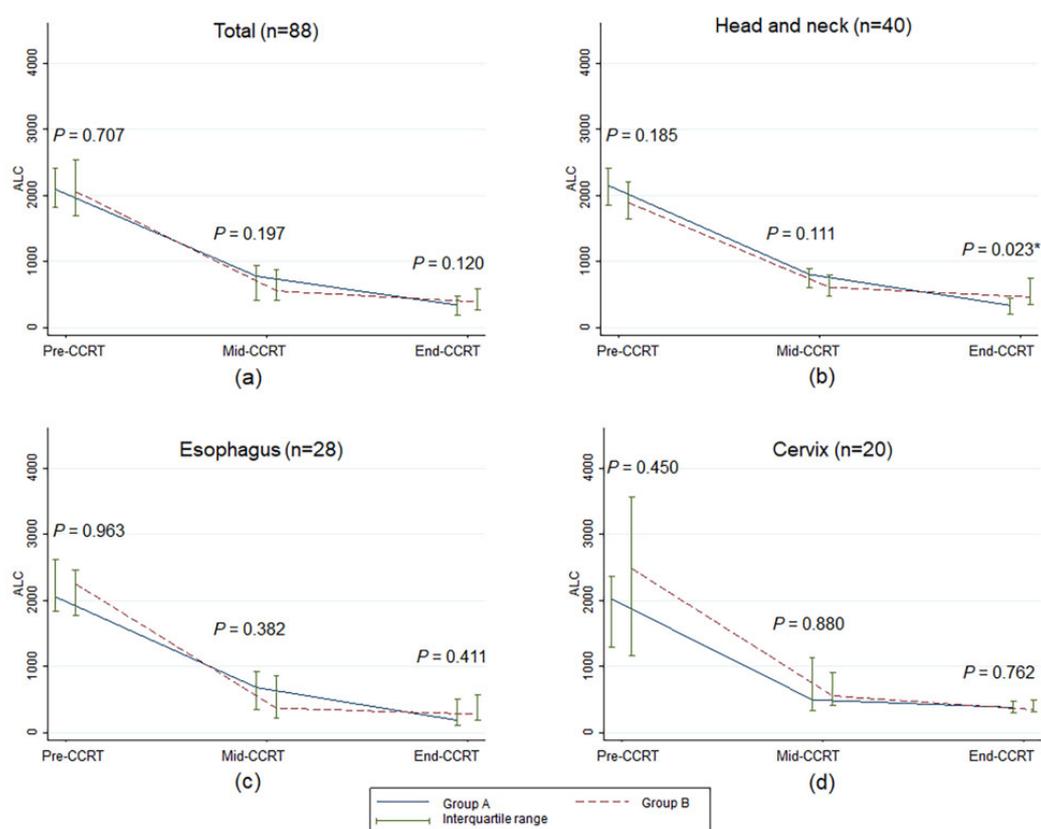

Fig. 2. Median and interquartile range of absolute lymphocyte count over time according to treatment visit of concurrent chemoradiotherapy. ALC, absolute lymphocyte count; P, P-value from the Mann-Whitney test to compare ALC between two groups at each treatment visit; *$P < 0.05$.

and NLR at end-CCRT increased 8.79 times compared to pre-CCRT (adjusted $\beta = 5.33$; 95% CI: 3.34–7.32; $P < 0.001$ and adjusted $\beta = 8.79$; 95% CI: 6.80–10.79; $P < 0.001$, respectively). There was a lower rate of NLR change over time in group B than group A, although the difference was not statistically significant. Table 4 reports the univariable and multivariable models to identify factors associated with ALC changes over time. In the multivariable model, ALC

after CCRT increased by 0.41 cells/μL (95% CI: 0.36–0.46) for each unit increase in pre-CCRT ALC in which a higher ALC at pre-CCRT was significantly associated with a higher ALC after CCRT ($P < 0.001$). ALC was significantly decreased by 1,463.87 cells/μL at mid-CCRT (adjusted $\beta = -1,463.87$; 95% CI: −1,598.49 to −1,329.25; $P < 0.001$), and 1,692.18 cells/μL at end-CCRT (adjusted $\beta = -1,692.18$; 95% CI: −1,827.09 to −1,557.27; $P < 0.001$) compared to pre-CCRT.

Table 3
Factors associated with neutrophil to lymphocyte ratio change overtime using generalized estimation equation models

Variables	Univariable analysis			Multivariable analysis		
	β	95% CI of β	P	adj β	95% CI of β	P
Arm						
Group A [ref.]						
Group B	−1.57	−3.48 to 0.34	0.107	−1.29	−2.96 to 0.39	0.132
NLR at pre-CCRT	1.06	0.62 to 1.50	< 0.001	1.08	0.64 to 1.52	< 0.001
Treatment visits of CCRT						
Pre-CCRT [ref.]						
Mid-CCRT	5.34	3.35 to 7.33	< 0.001	5.33	3.34 to 7.32	< 0.001
End-CCRT	8.73	6.74 to 10.73	< 0.001	8.79	6.80 to 10.79	< 0.001
Cancer site						
Cervical cancer [ref.]						
Head and neck cancer	−0.56	−3.01 to 1.89	0.653	0.76	−1.44 to 2.96	0.498
Esophageal cancer	0.83	−1.81 to 3.47	0.537	1.21	−0.36 to 4.31	0.097
Age [years]	0.06	−0.03 to 0.14	0.184			
BMI [kgm^2]	−0.11	−0.38 to 0.16	0.431			
Gender						
Female [ref.]						
Male	0.12	−1.82 to 2.07	0.901			

Abbreviations: 95% CI, 95% confidence interval; β, regression coefficient; adj β, adjusted regression coefficient; BMI, body mass index; CCRT, concurrent chemoradiotherapy; NLR, neutrophil to lymphocyte ratio; P, P-value from the Wald test; ref., reference group.

Table 4
Factors associated with absolute lymphocyte count change overtime using generalized estimation equation models

Variables	Univariable analysis			Multivariable analysis		
	β	95% CI of β	P	adj β	95% CI of β	P
Arm						
Group A [ref.]						
Group B	3.20	−144.08 to 150.48	0.966	4.78	−66.87 to 76.42	0.896
ALC at pre-CCRT	0.40	0.35 to 0.45	< 0.001	0.41	0.36 to 0.46	< 0.001
Treatment visits of CCRT						
Pre-CCRT [ref.]						
Mid-CCRT	−1,461.62	−1,596.15 to −1,327.10	< 0.001	−1,463.87	−1,598.49 to −1,329.25	< 0.001
End-CCRT	−1,687.10	−1,822.08 to −1,552.11	< 0.001	−1,692.18	−1,827.09 to −1,557.27	< 0.001
Cancer site						
Cervical cancer [ref.]						
Head and neck cancer	12.64	−174.52 to 199.81	0.895	24.65	−66.51 to 115.82	0.596
Esophageal cancer	30.46	−172.41 to 233.34	0.769	−61.35	−160.51 to 37.80	0.225
Age [years]	−1.25	−7.72 to 5.22	0.705			
BMI [kgm^2]	13.47	−6.90 to 33.84	0.195			
Gender						
Female [ref.]						
Male	−78.47	−225.53 to 68.59	0.296			

Abbreviations: 95% CI, 95% confidence interval; β, regression coefficient; adj β, adjusted regression coefficient; ALC, absolute lymphocyte count; BMI, body mass index; CCRT, concurrent chemoradiotherapy; P, P-value from the Wald test; ref., reference group.

However, the degree of ALC change over time between group A and group B was not statistically significant. Nevertheless, in the head and neck cancer subgroup, ALC at end-CCRT in group B was significantly higher than in group A (median ALC of 465.95 cells/μL vs. 342.80 cells/μL ($P = 0.023$), respectively). The results of GEE model for head and neck cancer patients showed the degree of NLR and ALC change over time between group A and group B were not statistically sig-

nificant (Supplementary Tables S2 and S3). For the type of tumors (i.e., oropharynx, hypopharynx, nasopharynx, and oral), no statistical associations to NLR and ALC changes over time were detected.

4. Discussion

Several markers are routinely used to evaluate nutrition status of patients. Serum albumin is one of nutrition

parameters commonly used in clinical practice which may predict prognosis of patients. For example, hepatocellular carcinoma patients with low serum albumin level resulted in a worsening liver function and poor clinical outcomes [36]. In addition, white blood cells including neutrophils and lymphocytes are frequently measured in cancer patients, particularly during active anticancer treatment. In this study, we demonstrated the dynamic changes of practical prognostic factors for inflammation and immunity by using NLR and ALC calculated from CBC, which is a routine laboratory test. We also showed the effect of immune-enhancing nutritional supplementation on NLR and ALC during CCRT.

NLR significantly increased throughout the course of CCRT for all cancer types, which signifies increasing inflammation as an undesirable effect of both radiotherapy and chemotherapy treatment. Our finding is consistent with Sunpaweravong et al. [37], who evaluated the anti-inflammatory effect of immune-enhancing nutrition on esophageal cancer during CCRT by using C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) as markers; they found that both inflammatory markers rose during CCRT. Machon et al. [38] evaluated the efficacy of immune-enhancing nutritional supplementation at 5 days before CCRT and 5 days before each cycle of chemotherapy during radiotherapy of head and neck cancer. Their results show that the median CRP was lower after the first cycle of 5 days of supplementation compared to the baseline. However, they did not find a significant change in median CRP between the first cycle of immune-enhancing nutritional supplementation and the end of radiotherapy. Ou et al. [39] demonstrated similar result of significant rising of NLR through radiotherapy course and verified that post-RT NLR was associated with 5-year overall survival (OS) and progression-free survival (PFS) in nasopharyngeal cancer.

Median ALC at pre-CCRT of all patients in the present study was 2,070 cells/μL, which is within the normal range. However, ALC decreased significantly from its pre-CCRT level throughout the whole course of CCRT to 616 and 377 cells/μL at mid-CCRT and end-CCRT, respectively, in all patients. This occurrence was also seen for all three cancer sites. Our finding is consistent with a sub-cohort of head and neck cancer patients receiving CCRT in the study by Ho et al. [34]. This group of patients had statistically significant decreased white blood cell count, and neutrophil and lymphocyte percentages after CCRT; their mean ALC levels before and after CCRT were 1,400 cells/μL and 300 cells/μL

($P < 0.001$), respectively. Campian et al. [40] discovered that the total lymphocyte count dropped rapidly from the normal value before CCRT to < 500 cells/μL only 2 months after starting CCRT for head and neck cancer. This is in line with the ALC in the head and neck cancer patients in our study, which dramatically lowered during the course of CCRT from 2,042 cells/μL at pre-CCRT to 685 and 421 cells/μL at mid-CCRT and end-CCRT, respectively. Furthermore, we also had similar results for the sub-cohort of esophageal and cervical cancers.

Based on the results of our study, radiotherapy and chemotherapy had a significant adverse effect on NLR and ALC during CCRT. Radiotherapy induces both apoptosis and non-apoptotic cell death to cancer cells. Apoptosis is a power-driven form of cell death that is either controlled or initiated in reaction to particular stimuli (e.g., cytokines) [41] or stimulated by cellular stress or injury [42]. Turrel et al. [43] summarized that the decline in ALC observed in cancer patients could be caused by a decreased production of lymphocytes. Chemoradiotherapy also significantly increases inflammation, and damage-associated molecular patterns are present after tissue damage from the radiation and activated pro-inflammatory immune system [44]. Elevated inflammatory cytokines also have been reported in cancer treated with radiotherapy and chemotherapy [45,46]. In our multivariate analysis, pre-CCRT NLR and pre-CCRT ALC were associated with NLR and ALC values during CCRT, respectively. Moreover, the time point during CCRT was associated with both NLR and ALC levels. Thus, we should keep NLR at pre-CCRT as low as possible and ALC at pre-CCRT before CCRT as high as possible.

Apart from the inflammation marker, NLR is used as a prognostic factor in cancers. Higher pretreatment NLR is correlated with worse OS in oropharyngeal cancer treated and worse disease-free survival and OS in esophageal cancer with radiotherapy [47–49]. High post-RT NLR is associated with poor OS and PFS in nasopharyngeal cancer and higher recurrent rate in breast cancer [39,50]. Similarly, ALC is used as prognosis factor and nutritional status assessment. Low post-RT ALC links to the deteriorated OS in oropharyngeal cancer [51]. ALC is also used as a part of the formulae to evaluate nutritional status which also associates with prognosis in cancer patient. Serum albumin and ALC are used to calculate prognostic nutritional index (PNI). The same lab tests with an additional ratio of current weight and ideal body weight are used for Geriatric Nutritional Risk Index (GNRI). Caputo

et al. [52] demonstrated that low PNI (< 31.3) was associated with poor OS in hepatocellular carcinoma treated with Sorafenib. Sasaki et al. [53] evaluated elderly patients with colorectal cancer underwent surgery and found the correlation between low GNRI ($\leqslant 98$) and higher postoperative complications and lower OS. The benefit of immune-enhancing nutrition on NLR and ALC was not proven in this study. However, we found that the increase in NLR during CCRT was less steep in the immune-enhancing nutritional supplementation group. The drop in percentage change of ALC was also lower in patients who received the supplementation but the difference was not statistically significant. Still, in the head and neck cancer patients, ALC at the end-CCRT was significantly higher in patients receiving immune-enhancing nutrition compared to the control group. Since NLR and ALC are sensitive markers for several conditions (e.g., infection, surgery, cancer, etc.), changes in both markers for monitoring the effect of immune-enhancing nutritional supplementation might have been obscured by co-determiners. In addition, we enrolled patients with several different sites of cancer that can have different degrees of inflammation, thereby making our results inconsistent [54].

Another study using different and more novel inflammatory markers (CRP and TNF-α) than in our study revealed the benefits of immune-enhancing nutritional supplementation [37]. The authors found that the rise in CRP/TNF-α ratio from its pre-CCRT level was significantly lower in the immune-enhancing nutrition group [37]. Our previous study on clinical outcomes also showed that the immune-enhancing nutritional supplementation group was accompanied by a lower grade of hematologic toxicity [9]. These results imply the benefit of immune-enhancing nutritional supplementation even though there was no significant difference in NLR and ALC levels in our recent study.

Immune-enhancing nutrition may be one of key facet in cancer management. Other novel treatment might also be beneficial. Metronomic approach may be associated with improved nutritional status in patients with head and neck cancer [55] as well as patients with hepatocellular carcinoma [56].

This study has some limitations, the first being the diversity of cancer sites, as mentioned previously, since the values of NLR and ALC vary in the different primary cancers [57,58]. A focused study on each particular cancer site might reveal more detail on the dynamic changes of these values. The second potential limitation is that we did not measure other more novel inflammation markers such as CRP, interleukin-6 (IL-6), and TNF-α. However, this could also be viewed as a strength in that we monitored the inflammation and immunity status of the patients with only a simple blood test (CBC) taken once a week during CCRT which was a real-world clinical practice circumstance. Formulae that assess immunonutrition status such as PNI or GNRI which use simple blood test (CBC, serum albumin) can also be used in further study.

Our results indicate that the pre-CCRT NLR and ALC values were affected by CCRT, thereby confirming the results of Machon et al. [38] that immune-enhancing nutritional supplementation before CCRT can lower these inflammation markers. A future study to confirm that immune-enhanced nutritional supplementation improves these pre-CCRT inflammation and immunity marker is being planned as a prospective trial.

The recovery of NLR and ALC after CCRT also a potential subject for further investigation. Since we did not measure ALC and NLR during follow-up after CCRT and immune-enhancing nutritional supplementation was stopped immediately at the end of CCRT, the effect of the supplementation in this period cannot be evaluated. This is one of the limitations of our study and it would be interesting to investigate whether allowing continual immune-enhancing nutritional supplementation would enable recovery from treatment-related lymphopenia caused by CCRT since it takes some time for the normal cells to recover from the effects of both treatment modalities.

5. Conclusions

Dynamic detrimental changes in NLR and ALC levels were demonstrated throughout CCRT. Pre-CCRT values of both markers were significant predictors for a favorable change. There were noticeable promising changes in both NLR and ALC values in patients receiving immune-enhancing nutritional supplementation, although the differences were not statistically significant. The effect of immune-enhancing nutritional supplementation on pre-CCRT NLR and ALC should be evaluated in a future randomized study.

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Supplementary data

The supplementary files are available to download from http://dx.doi.org/10.3233/CBM-210086.

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