ANTICANCER RESEARCH *41*: 4471-4478 (2021)
doi:10.21873/anticanres.15256

Neutrophil-to-lymphocyte Ratio as a Prognostic Factor for Colon Cancer in Elderly Patients: A Propensity Score Analysis

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Abstract. *Aim: This study aimed to evaluate the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in elderly patients with Stage I-III colon cancer for long-term oncologic outcomes. Patients and Methods: We retrospectively reviewed 175 patients aged >75 years who underwent radical surgery for Stage I-III colon cancer between 2000 and 2015 at our institute. Overall survival (OS), cancer-specific survival (CSS), and relapse-free survival (RFS) were evaluated according to NLR values using propensity score analysis. Patients were allocated to the higher NLR (H-NLR) or the lower NLR (L-NLR) group with a cut-off value of 2.3, based on receiver operating characteristic curve. Results: Before case matching, there were significant differences between the two groups for CSS (p=0.023) and RFS (p<0.001), but not for OS (p=0.069). Similar results were obtained after case matching, with significant differences observed for CSS (p=0.003) and RFS (p=0.027), but not for OS (p=0.145). Conclusion: NLR may be a prognostic factor in elderly patients with colon cancer.*

Colon cancer surgery for elderly patients is becoming increasingly common as the elderly population continues to grow worldwide. There is usually no hesitation in deciding on a treatment plan for resectable colon cancer. However, elderly patients often have several comorbidities and dysfunctional status, which can result in higher morbidity and mortality after surgery compared with younger patients (1, 2), making decisions regarding treatment strategy difficult. Thus, it is important to assess the general condition of elderly patients preoperatively in order to predict long-term oncologic outcomes.

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Key Words: Nneutrophil-to-lymphocyte ratio, NLR, elderly patients, propensity score matching, colon cancer.

There are various risk assessment tools to assess the general condition of elderly patients [*e.g.*, American Society of Anesthesiologists' (ASA) class (3), Charlson comorbidity index (4), the National Institute on Aging (NIA) and the National Cancer Institute (NCI) (5), the sum of diseased organ systems (SDOS) (6)]. We previously reported that neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor for both overall survival (OS) and relapse-free survival (RFS) in Stage II-III colon cancer patients of all ages (7). However, there was no reports assessing NLR focused solely on elderly patients.

In this regard, this study aimed to evaluate the prognostic value of NLR in elderly patients with Stage I-III colon cancer for long-term oncologic outcomes using propensity score analysis.

Patients and Methods

Patients. We retrospectively reviewed 175 patients aged >75 years who were performed radical surgery for Stage I-III colon cancer between 2000 and 2015 at our hospital. All patients underwent curative surgery. We divided patients into two groups according to NLR values: lower NLR (L-NLR) and higher NLR (H-NLR) groups. Using receiver operating characteristic (ROC) curve analyses, we set 2.3 as a cut-off of NLR value for death, recurrence, and cancer-specific death [death: area under the curve (AUC)=0.582; 95% CI=0478-0.686; recurrence: AUC=0.716; 95% CI=0.613-0.819; cancer-specific death: AUC=0.573; 95% CI=0.474-0.672]. NLR values were usually checked on the day patients first visited the outpatient department. The present study was approved by the institutional review board of Tokyo Medical University Hospital.

Postoperative systemic adjuvant chemotherapy. At our institute, we generally perform adjuvant chemotherapy (AC) for patients aged <80 years with pathological Stage III colon cancer. For patients aged ≥80 years, postoperative systemic AC may be performed depending on the general condition of the patient. In our study, we performed AC in 15 of 89 (16.9%) patients who had pStage II cancer and 37 of 82 (45.1%) patients who had pStage III cancer. We commonly used Oxaliplatin-based or 5-fluorouracil-based regimens.

Follow-up. The median follow-up period was 63.3 months (range=0.2-186.6 months). We followed patients who had Stage II

or III cancer for up to five years after operation. Tumor marker was measured every three months and we performed a CT scan every six months. We recorded the recurrence site and date the recurrence occurred.

Statistical analysis. We set the primary outcomes as 5-year OS, 5-year RFS and 5-year cancer-specific survival (CSS). We defined OS as the number of days between the operation and either death or the end of the observation period. We censored patients who were alive at the end of the follow-up period. We defined RFS as the number of days between operation and either recurrence or death from underlying disease. We defined CSS as the number of days between operation and either death from colon cancer or the end of the observation period. Patients who died from a cause other than colon cancer were censored. We used the Kaplan-Meier method for survival characteristics and used the log-rank test.

We performed propensity score analyses to minimize bias. We used multivariate logistic regression to create a propensity score to predict condition according to NLR value (NLR >2.3 or ≤2.3). Nine covariates were assessed such as sex, body mass index (BMI), pathological T-stage, pathological N-stage, pathological stage, ASA-performance status (PS), Charlson Comorbidity Index (CCI), tumor location (sidedness) and adjuvant chemotherapy (AC). We attached each patient with a propensity score. Each patient with a NLR <2.3 (L-NLR) was matched to a patient with a NLR ≥2.3 (H-NLR) and had the closed propensity score on the logit scale with a caliper of 0.05. Using propensity score, we performed propensity score matching and regression analysis.

We used SPSS software (IBM SPSS Statistics for Windows, Version 26.0; IBM, Chicago, IL, USA) for all statistical analysis. We set the value for statistical significance at $p<0.05$.

Table I. *Baseline characteristics*.

Factor		N (n=175)
Gender	Female	74 (42.3)
	Male	101 (57.7)
BMI, kg/m^2	<25	144 (82.3)
	≥25	31 (17.7)
PS	0	133 (76.0)
	1	29 (16.6)
	2	11 (6.3)
	3	2 (1.1)
CCI	<5	96 (54.9)
	≥5	79 (45.1)
T-Stage	1	2 (1.1)
	2	6 (3.4)
	3	142 (81.1)
	4	25 (14.3)
N-Stage	0	93 (53.1)
	1-3	82 (46.9)
pStage	I	3 (1.7)
	II	89 (51.1)
	III	82 (47.1)
Sidedness	Right	101 (57.7)
	Left	74 (42.3)
Adj.	No	118 (69.4)
	Yes	52 (30.6)

Data are expressed as median (range) or n (%). NLR: Neutrophil-to-lymphocyte ratio; BMI: body mass index; PS: performance status; CCI: Charlson Comorbidity Index; AC: adjuvant chemotherapy.

Results

NLR. For the entire cohort (n=175), the median NLR was 2.6 (range=0.2-47.9) and there were 84 patients in the L-NLR group and 91 patients in the H-NLR group. After case matching (n=116), the median NLR was 1.75 (range=0.6-2.3) in the L-NLR group (n=58) and 3.92 (range=2.45-22.3) in the H-NLR group (n=58).

Patient and tumor characteristics. Table I shows baseline characteristics. There were significantly more females in the L-NLR group compared to the H-NLR group (51.2% vs. 34.1%, $p=0.033$). There were no significant differences between the two groups for the other assessed covariates.
According to propensity scores, we performed matched analysis to adjust for uneven distribution in the L-NLR and H-NLR groups, using nine covariates [*i.e.*, sex, BMI, pathological T-stage, pathological N-stage, pathological stage, ASA-PS, CCI, tumor location (sidedness) and adjuvant chemotherapy]. Figure 1A and 1B shows the distributions of the propensity scores. A well-matched distribution with respect to patient and tumor characteristics after case matching was found between L-NLR and H-NLR groups (58 matched pairs) (Table II). There was no significant difference between the two groups.

Regression adjustment including propensity scores. We applied a propensity score to create a Cox model that adjusts for differences between two groups through regression adjustment. In the entire cohort (n=175), hazard ratios (HRs) for OS, RFS, and CSS in the L-NLR group relative to the H-NLR group were 1.82 (95% CI=0.9447-3.505), 1.848 (95% CI=1.08-3.164) and 5.108 (95% CI=1.744-14.96), respectively (Table III).

OS and RFS rates. In the entire cohort, 5-year OS, 5-year RFS and 5-year CSS rates were 81.6%, 88.3% and 83.1%, respectively. 5-year OS, RFS and CSS rates were 80.7%, 89.2% and 92.4% in the L-NLR group (n=84), respectively, and 79.2%, 75.8% and 81.1% in the H-NLR group (n=91), respectively. Significant differences were observed between the two groups for CSS and RFS ($p=0.023$ and 0.001, respectively), but not OS ($p=0.069$) (Figure 2).

The results of survival outcomes after case matching were similar with significant differences observed between the two groups for CSS (L-NLR group: 97.6%; H-NLR group: 81.8%; $p=0.003$) and RFS (L-NLR group: 88.5%; H-NLR group: 75.9%; $p=0.027$), but not OS ($p=0.145$) (Figure 3A-C).

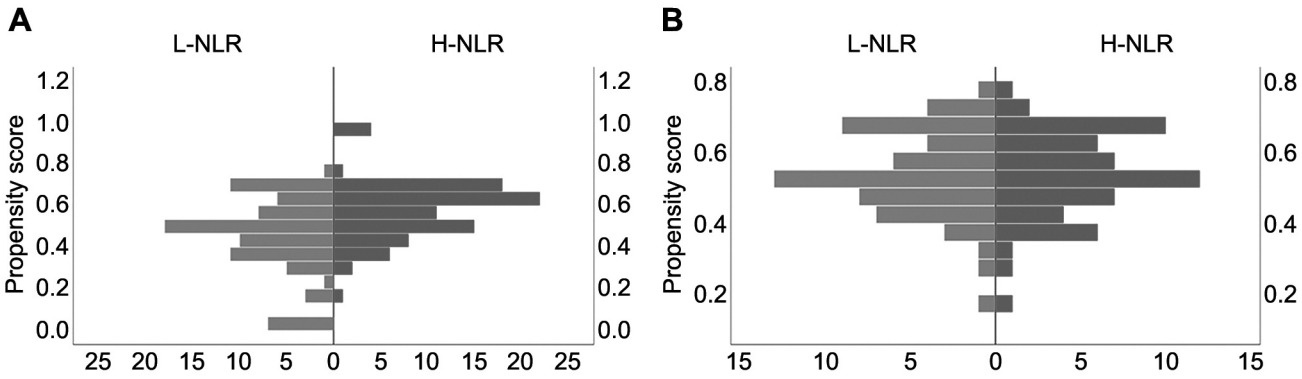

Figure 1. *Distributions of propensity scores before and after case matching. (A) Distribution of propensity scores in the entire cohort. (B) Distribution of propensity scores in the propensity score-matched cohort.*

Table II. *Characteristics of both the entire cohort and the propensity score-matched pairs.*

	Entire cohort (n=175)			Propensity score-matched pairs (n=118)		
Factor	L-NLR (n=84)	H-NLR(n=91)	*p*-Value	L-NLR(n=58)	H-NLR(n=58)	*p*-Value
n	84	91		58	58	
Gender			0.033			1
Female	43 (51.2)	31 (34.1)		26 (44.8)	25 (43.1)	
Male	41 (48.8)	60 (65.9)		32 (55.2)	33 (56.9)	
BMI, kg/m^2			0.521			0.798
<25	67 (79.8)	77 (84.6)		50 (86.2)	48 (82.8)	
≥25	17 (20.2)	14 (15.4)		8 (13.8)	10 (17.2)	
PS			0.929			0.758
0	62 (73.8)	71 (78.0)		44 (75.9)	45 (77.6)	
1	15 (17.9)	14 (15.4)		9 (15.5)	8 (13.8)	
2	6 (7.1)	5 (5.5)		5 (8.6)	4 (6.9)	
3	1 (1.2)	1 (1.1)		0 (0.0)	1 (1.7)	
CCI			1			0.709
<5	46 (54.8)	50 (54.9)		33 (56.9)	30 (51.7)	
≥5	38 (45.2)	41 (45.1)		25 (43.1)	28 (48.3)	
T-Stage			0.067			1
1	1 (1.2)	1 (1.1)		49 (84.5)	50 (86.2)	
2	6 (7.1)	0 (0.0)		8 (13.8)	7 (12.1)	
3	64 (76.2)	78 (85.7)		35 (60.3)	36 (62.1)	
4	13 (15.5)	12 (13.2)		23 (39.7)	22 (37.9)	
N-Stage			0.966			1
0	44 (52.4)	49 (53.8)		32 (55.2)	32 (55.2)	
1 - 3	40 (47.6)	42 (46.2)		26 (44.8)	26 (44.8)	
pStage			0.157			0.962
I	3 (3.6)	0 (0.0)		32 (55.2)	32 (55.2)	
II	40 (47.6)	49 (54.4)		26 (44.8)	26 (44.8)	
III	41 (48.8)	41 (45.6)		1 (1.7)	1 (1.7)	
Sidedness			0.764			1
Right	47 (56.0)	54 (59.3)		35 (60.3)	36 (62.1)	
Left	37 (44.0)	37 (40.7)		23 (39.7)	22 (37.9)	
Adj.			0.215			0.838
No	52 (64.2)	66 (74.2)		42 (72.4)	40 (69.0)	
Yes	29 (35.8)	23 (25.8)		16 (27.6)	18 (31.0)	

Data are expressed as median (range) or n (%). NLR: Neutrophil-to-lymphocyte ratio; BMI: body mass index; PS: performance status; CCI: Charlson Comorbidity Index; AC: adjuvant chemotherapy; L-NLR: low-neutrophil-to-lymphocyte ratio group; H-NLR: high-neutrophil-to-lymphocyte ratio group.

Table III. *Hazard ratios to measure the effects of neutrophil-to-lymphocyte ratio (NLR).*

A. Overall survival

	Sample size (no. patients)		Hazard ratio [95 % CI]
	L-NLR	H-NLR	
Unadjusted model	84	91	1.82 [0.94-3.51]
Propensity score-adjusted model			
Regression adjustment	84	91	1.77 [0.90-3.48]
Matching 1:1	58	58	2.42 [0.99-5.88]

B. Cancer-specific survival

	Sample size (no. patients)		Hazard ratio [95 % CI]
	L-NLR	H-NLR	
Unadjusted model	84	91	5.11 [1.74-14.96]
Propensity score-adjusted model			
Regression adjustment	84	91	4.62 [1.56-13.64]
Matching 1:1	58	58	12.52 [1.62-96.32]

C. Relapse-free survival

	Sample size (no. patients)		Hazard ratio [95 % CI]
	L-NLR	H-NLR	
Unadjusted model	84	91	1.85 [1.08-3.16]
Propensity score-adjusted model			
Regression adjustment	84	91	1.82 [1.05-3.16]
Matching 1:1	58	58	2.11 [1.07-4.15]

NLR: Neutrophil-to-lymphocyte ratio; L-NLR: low-neutrophil-to-lymphocyte ratio group; H-NLR: high-neutrophil-to-lymphocyte ratio group.

Discussion

A recent study showed that the median age at colorectal cancer diagnosis was 67 years, and 56.3% of all colorectal cancer cases were diagnosed in people aged >65 years, of whom 32% were aged >75 years. The WHO defines "elderly" as being aged >65 years. There is no evidence which clearly define the term "elderly" and there is limited evidence on how treatment recommendations apply to this elderly population. Many studies defined elderly patients with colorectal cancer as aged >70 or >75 years. NLR was first reported as a predictive factor for OS and CSS in colon cancer patients in 2005 (8). NLR, as a predictive factor in assessing the prognosis of patients with cancers from various types of cancers, has also been reported (9-13). But no study has focused solely on elderly patients.

Previous studies suggested that dissociation is recognized depending on age in colon cancer survival, with relatively lower survival rates for elderly patients (aged ≥75 years) compared with patients in all ages (14-16). In addition, while colon cancer survival has increased (16, 17), the improvements in survival rates for older patients tend to be stagnant, creating a large age gap in survival (14, 16). These poor survival rates for elderly patients may be a consequence of social environment (*i.e.*, social isolation or low socioeconomic status) (18, 19), patient factors (*i.e.*, comorbidities, frailty, lower tolerance of multimodality treatments) (20, 21), and healthcare factors (*i.e.*, suboptimal cancer management, diagnostic delay). In the present study, the RFS of elderly patients was comparable to that of patients with all ages, but OS was worse than that of patients of all ages in the entire cohort according to our past report (7).

For Stage III colon cancer, it is recommended to perform adjuvant chemotherapy regardless of age, but careful treatment is recommended for elderly patients (22). Yet, studies have shown that we tend not to perform adjuvant chemotherapy for elderly patients compared with younger patients (patients <75 years old) (23-25). In general, for advanced stage colon cancer, less intensive combination

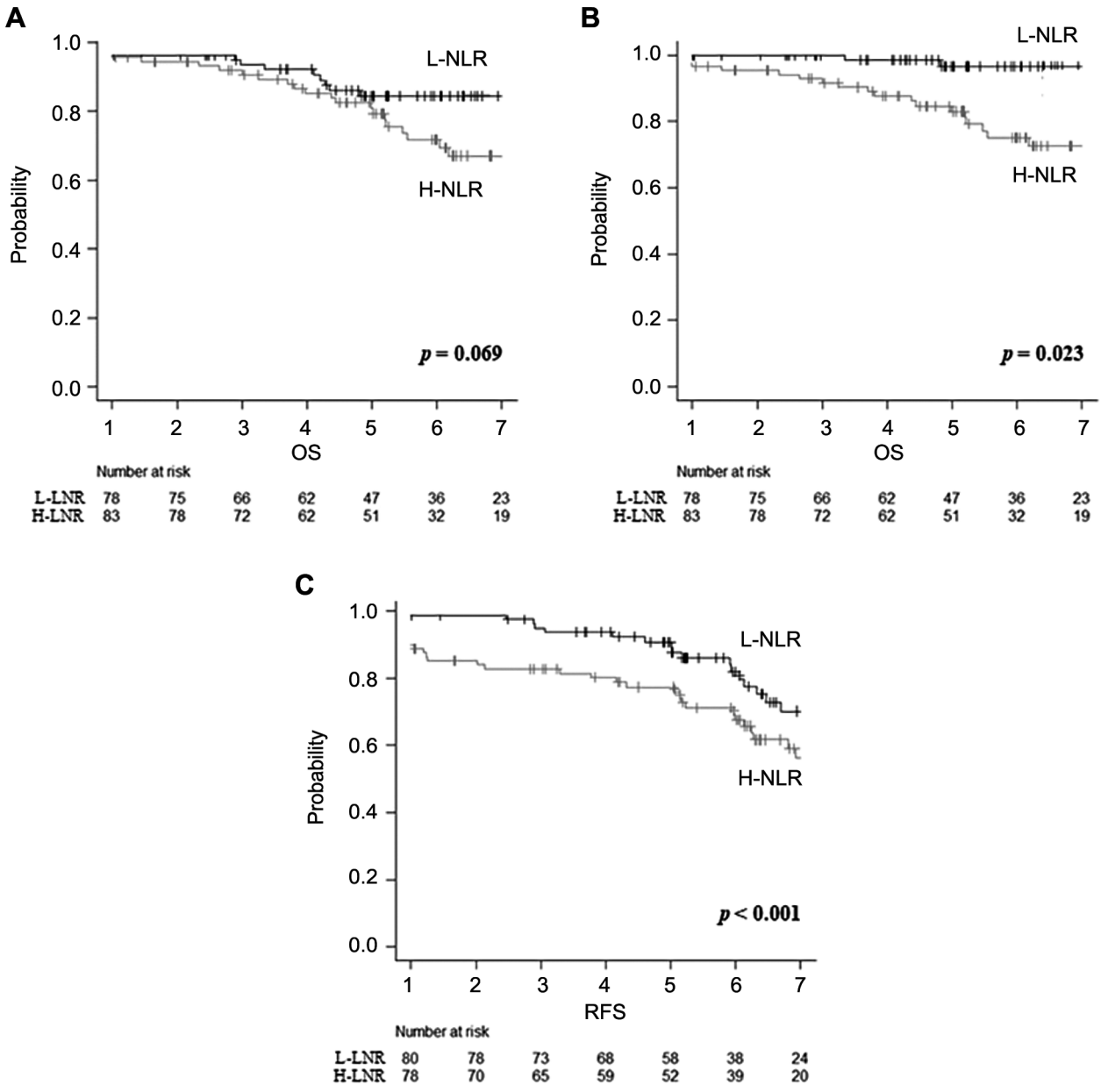

Figure 2. *Survival rates in the entire cohort (n=175). (A) Overall survival rates, (B) cancer-specific survival rates, and (C) relapse-free survival rates. Significant differences were observed between the L-NLR group and the H-LNR group for cancer-specific survival rates and relapse-free survival rates (p=0.023 and 0.001, respectively), but not overall survival rates (p=0.069) using the log-rank test.*

therapies are recommended for elderly patients who are unfit (26). Some evidence suggests that elderly patients who are fit can be prescribed the same regimen as younger patients (27, 28). In our study, although preoperative NLR was not correlated with OS, it was correlated with RFS and CSS, suggesting that NLR has little effect on oncological outcomes and can be used to identify which elderly patients should be prescribed performed adjuvant chemotherapy or not.

How the elderly spent their last days is very important, and some reports have shown that elderly patients with end-stage cancer have a worse quality of life (QOL) than those with earlier-stage cancer (29). Thus, from the viewpoint of QOL, cancer-free status is also important for these patients. Our findings highlight the potential benefits of extending CSS in elderly patients selected based on preoperative NLR, rather than avoiding chemotherapy altogether simply because the patient is elderly.

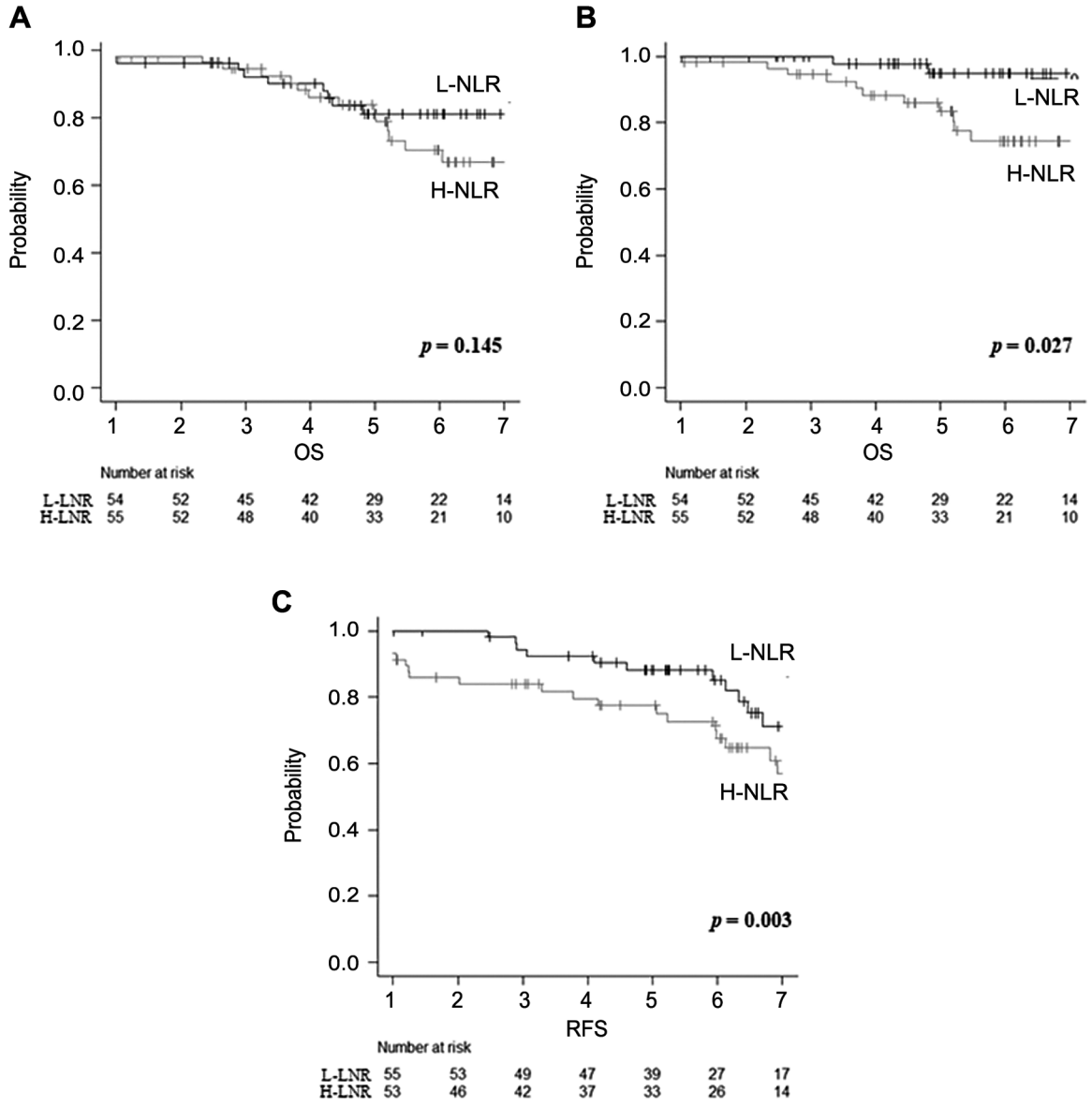

Figure 3. *Survival rates in the propensity score-matched cohort (n=118). (A) Overall-survival rates, (B) cancer-specific survival rates, and (C) relapse-free survival rates. Significant differences were observed between the L-NLR group and the H-LNR group for cancer-specific survival rates and relapse-free survival rates (p=0.027 and 0.003, respectively), but not overall survival rates (p=0.145) using the log-rank test.*

There are some limitations in this study. Firstly, this is a retrospective study. However, we used a propensity score analysis to minimize selection bias. Secondly, we did not use the cofounders such as hematologic or autoimmune disease, which could influence preoperative NLR values. Thirdly, there was no molecular assessment such as microsatellite instability. It will be important to perform a prospective study to further clarify the prognostic value of NLR in elderly patients.

In conclusion, it was suggested that NLR may be a prognostic factor in elderly patients with colon cancer in the present study. IT may be useful in determining perioperative treatment strategies for elderly patients with colon cancer.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

J.M. wrote the main manuscript text and H.S., R.U., T.T., K.K., H.K., M.E. and T.I. acquired data for the work. All authors reviewed the final manuscript. KK, YN and AT drafted the work or revised it critically for important intellectual content.

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Received May 27, 2021
Revised July 22, 2021
Accepted July 26, 2021