Inflammatory markers and overall survival in older adults with cancer

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ABSTRACT

Background: Our aim was to evaluate the prognostic impact of three inflammatory markers - neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and lymphocyte monocyte ratio (LMR) - on overall survival (OS) in older adults with cancer.
Materials and Methods: Our sample includes 144 patients age ≥ 65 years with solid tumor cancer who completed a cancer-specific Geriatric Assessment (GA) from 2010 to 2014 and had pretreatment CBC with differential. NLR was dichotomized a previously reported cut-off value of 3.5, while PLR and LMR were dichotomized at the median. Cox proportional hazards models evaluated whether NLR, PLR and LMR were predictive of OS independent of covariates including a recently developed 3-item GA-derived prognostic scale consisting of (1) "limitation in walking several blocks", (2) "limitation in shopping", and (3) "≥ 5% unintentional weight loss in 6 months".
Results: Median age was 72 years, 53% had breast cancer, 27% had stage 4 cancer, 14% had Karnofsky Performance Status (KPS) < 80, 11% received less intensive than standard treatment for stage, and 39% had NLR > 3.5. In univariable analysis, higher NLR and PLR and lower LMR were significantly associated with worse OS. NLR remained a significant predictor of OS (HR = 2.16, 95% CI; 1.10–4.25, $p = .025$) after adjusting for cancer type, stage, age, KPS, treatment intensity, and the GA-derived prognostic scale.
Conclusion: NLR > 3.5 is predictive of poorer OS in older adults with cancer, independent of traditional prognostic factors and the GA-derived prognostic scale.

1. Introduction

Inflammation is a hallmark of cancer development and progression [1]. The prognostic value of markers of inflammation, indicated by elevated levels of cytokines, C-reactive protein, and white blood cell counts (WBCs) and its subpopulations, has been demonstrated in various cancers [2]. Some inflammatory markers have been incorporated in prognostic tools for patients with cancer [3, 4]. In addition, routinely available biomarkers, such as neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and lymphocyte monocyte ratio (LMR) [5–7] have been shown to have robust prognostic value, independent of traditional variables such as age, cancer stage, and/or performance status [8–10].

In the general population of older adults, inflammatory markers are also predictors of adverse health outcomes including functional disability and all-cause mortality [11]. Chronic systemic inflammation is one of the key processes of aging, and has been termed "inflammageing" [12]. Physiologic aging can be categorized by geriatric assessment (GA) which evaluates functional status, nutrition, comorbidity, polypharmacy, cognition, psychological health, and social support [13]. Inflammatory markers have been found to be independent prognostic factors of survival after adjusting for GA-identified deficits in a general population of older adults [14].

The routine use of GA in older adults with cancer is recommended by the International Society of Geriatric Oncology and the National Comprehensive Cancer Network [15, 16]. One reason for this recommendation is that the GA is helpful to estimate prognosis in older adults with cancer [17]. Our research group has identified three measures in a cancer-specific GA to be prognostic of poorer survival, independent of cancer-related factors, age and performance status [18]. Using these three items ("limitation in walking several blocks", "limitation in shopping", and "≥ 5% unintentional weight loss in 6 months"), we constructed a three-item prognostic scale which correlates with overall survival (OS) and improves the prognostic accuracy of factors traditionally

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used in clinical practice. In this study, we evaluated the prognostic impact of the NLR, PLR and LMR on OS, independent of cancer type and stage, treatment, age, performance status and the GA-derived three-item prognostic scale.

2. Methods

2.1. Patient Population

The "Carolina Senior Registry" (CSR; ClinicalTrials.gov identifier NCT01137825) is a cross-sectional study of patients with cancer 65 years or older being treated in the outpatient setting who completed a cancer-specific GA [19]. Eligibility was restricted to patients able to speak and read English. The patients were recruited between October 2009 and September 2014. Informed consent was obtained from all patients prior to participation in the registry. Records of 546 patients in the CSR were linked to the North Carolina Central Cancer Registry (NCCCR) [20]. In this linked dataset, 179 patients completed a GA within 3 months of their date of cancer diagnosis. Of these patients, 144 patients had pretreatment complete blood count (CBC) and were included in this study. Patients with leukemia or acute infection at the time of baseline CBC test were excluded from our analysis. The NCCCR collects data on all cancers diagnosed in the state of North Carolina including date of diagnosis, cancer type, stage, and all-cause and cancer-specific mortality. If there were unspecified cancer-related variables (e.g. cancer type and stage) in the dataset, medical records were reviewed for clarification. Additional treatment data were extracted from medical records. Survival status was determined through linking to the National Death Index, Social Security Death Index, and North Carolina State Center for Vital Statistics, through August 2015. The patients who remained alive on August 31, 2015, were censored. The study protocol was approved by the University of North Carolina Institutional Review Board.

2.2. Study Measures

Inflammatory markers.

Pretreatment neutrophil, monocyte, lymphocyte, and platelet counts were abstracted from medical records. Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and lymphocyte monocyte ratio (LMR) were assessed as the independent variables. The NLR was dichotomized at 3.5 which was the upper boundary of 95% confidence interval (CI) observed in a healthy adult population [21]. A similar reference value has not yet been established for the PLR or LMR; therefore, these variables were dichotomized at the median.

GA-derived prognostic scale.

Our previous study identified three items from the cancer-specific GA that were strong significant prognostic factors for OS in older adults with cancer, independent of the traditional factors (cancer type, stage, age, and performance status) [18]. These items were: (1) "limitation in walking several blocks", (2) "limitation in shopping", and (3) "≥ 5% unintentional weight loss in 6 months". Using these items, we constructed a three-item prognostic scale (score ranging 0–3) to define four groups with markedly different survival probabilities. Using patients with no GA-identified deficits as a reference, the hazard ratio (HR) for mortality was 1.85 (95% CI 1.25–2.74) for patients with one deficit, 2.97 (95% CI 1.84–4.78) for patents with two deficits, and 8.67 (95% CI 4.97–15.15) for patients with three deficits. The three-item scale improved prognostic discrimination over the traditional variables alone.

2.3. Statistical Analysis

Descriptive statistics were used to describe baseline characteristics of the sample. The primary outcome was overall survival measured from the date of cancer diagnosis to date of death. Survival was estimated using the Kaplan Meier method and survival curves were compared using the log rank test. We examined bivariable associations between the outcome variable and each inflammatory marker (NLR, PLR and LMR). Multivariable Cox proportional hazards models were used to assess the independent effects of inflammatory markers on OS. Covariates were age (≥72 vs <72 years), physician-rated Karnofsky Performance Status (KPS; <80 vs ≥80), cancer type (breast vs other cancer), and cancer stage (stage IV vs I, II and III), treatment intensity (less intensive treatment vs standard treatment), and the GA-derived prognostic scale (continuous variable). For stage I-III disease, standard treatment was defined as surgery or definitive radiation with or without adjuvant therapy. For stage IV disease, standard treatment was defined as systemic therapy. If patients with stage I-III cancer receive palliative intent radiation or systemic therapy alone or patients with stage IV cancer receive best supportive care alone as their initial treatment, they were classified as "less intensive than standard treatment for stage". We performed bivariable analyses between NLR, LMR and PLR and covariates using chi-square test or Fisher's exact test. We built two multivariable models; a "traditional model" adjusting for cancer type, stage, age, KPS, and treatment intensity and a "fully adjusted model" adjusting

Table 1
Patient Characteristics.

Characteristic	No. of Patients ($n = 144$)	% Patients
Age, years		
65–69	54	38%
70–74	40	28%
75–79	20	14%
80–84	20	14%
≥ 85	10	7%
Sex		
Female	112	78%
Male	32	22%
Race		
White	130	90%
Other	14	10%
Educational level		
Highschool graduate or less	65	45%
Associate/Bachelor's	31	22%
Advanced degree	47	33%
Cancer type		
Breast	77	53%
Lung	27	19%
Gastrointestinal	12	8%
Genitourinary	10	7%
Head and Neck	12	8%
Other	6	4%
Cancer Stage		
Stage I	33	23%
Stage II	39	27%
Stage III	33	23%
Stage IV	39	27%
Physician-rated KPS		
100	60	42%
80–90	64	44%
60–70	14	10%
≤ 50	6	4%
Treatment Intensity		
Standard	128	89%
Less	16	11%
GA-derived prognostic scale		
0	65	45%
1	41	28%
2	29	20%
3	9	6%
Inflammatory Markers	Mean (SD)	Median
Neutrophils ($10^3/mm^3$)	5.20 (2.39)	4.80
Lymphocytes ($10^3/mm^3$)	1.60 (0.67)	1.50
Monocytes ($10^3/mm^3$)	0.45 (0.23)	0.40
Platelets ($10^3/mm^3$)	284 (101)	261
NLR	3.88 (2.60)	3.00
PLR	209 (128)	170
LMR	4.13 (2.03)	3.82

Abbreviations: KPS, Karnofsky performance status; LMR, lymphocyte monocyte ratio: NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SD, standard deviation.

Table 2
GA-derived three item prognostic scale.

Variable	Response	Score	No.	%
MOS-ADL				
Walking several blocks	Limited a little/Limited a lot	1	64	44%
	Not limited at all	0	80	56%
IADL				
Shopping	With some help/Unable	1	29	20%
	Without help	0	115	80%
Nutrition				
Unintentional weight loss over the past 6 months	≥ 5%	1	34	24%
	< 5%	0	110	76%

Abbreviations: IADL, instrumental activities of daily living; GA, Geriatric Assessment; MOS, Medical Outcomes Study.

for cancer type, stage, age, KPS, treatment intensity, and the GA-derived prognostic scale.

As exploratory analysis, we assessed the prognostic value of inflammatory markers for cancer-specific survival. We performed a subgroup analysis in patients with non-metastatic cancer as approximately 75% of patients had stage I-III disease in this cohort. Finally, we further evaluated the effects of inflammatory markers on OS, independent of GA measures which were previously reported to be prognostic of survival. These are activities of daily living (ADL; none vs ≥ one limitation) [21], instrumental activities of daily living (IADL; none vs ≥ one limitation) [22], Timed Up and Go test (TUG; ≤20 vs >20) [23], polypharmacy (a number of prescription drugs ≤3 vs >3) [24], five-item Mental Health Index (MHI5; ≥80 vs <80) [21], a number of comorbidity (<2 vs ≥3) [25], and unintentional weight loss in 6 months (<5 vs ≥5%) [26].

Analyses were performed using Stata 14 software (College Station, TX: StataCorp LP).

3. Results

3.1. Patient Characteristics

Table 1 presents the patient characteristics of 144 older adults with cancer. Median age was 72 years (range 65 to 91) and 78% were female. The most common type of cancer was breast cancer (53%) and 27% patients had a stage IV cancer. Most patients had a physician-rated KPS of 80 or greater (86%), with a range of 40 to 100. Eleven percent of patients received less intensive than standard treatment for stage. The baseline characteristics of the 144 patients were similar to those in the overall CSR-NCCCR cohort excluded from this study: median age 72 years (p = .48), 48% breast cancer (p = .22), 23% stage IV cancer (p = .72), and 85% physician-rated KPS ≥ 80 (p = .83). Median score for the GA-derived prognostic scale was 1 (range 0 to 3). The number of patients with each scoring variable used in the GA-derived prognostic scale is presented in Table 2. Median NLR, PLR and LMR values were 3.0, 169.7 and 3.8, respectively (Table 1). Using the pre-defined cut-off of 3.5, high NLR was identified in 56 patients (39%).

Table 3
Univariable Survival Analysis.

Variable	HR	95% CI	P value
Cellular markers of inflammation			
NLR; > 3.5 vs ≤ 3.5	5.08	2.85–9.07	< 0.001
LMR; > 3.8 (median) vs ≤ 3.8	2.11	1.21–3.66	0.008
PLR; > 170 (median) vs ≤ 170	2.10	1.20–3.67	0.009
Traditional prognostic factors			
Age; ≥ 72 vs < 72	1.25	0.73–2.13	0.423
Physician-rated KPS; < 80 vs ≥ 80	3.49	1.91–6.36	< 0.001
Cancer type; Breast vs Other	0.10	0.05–0.21	< 0.001
Stage; IV vs I - III	5.44	3.13–9.46	< 0.001
Treatment intensity; less vs standard	4.01	2.08–7.74	< 0.001
Geriatric assessment			
Three-item prognostic scale	1.94	1.48–2.53	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; LMR, lymphocyte monocyte ratio: NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio.

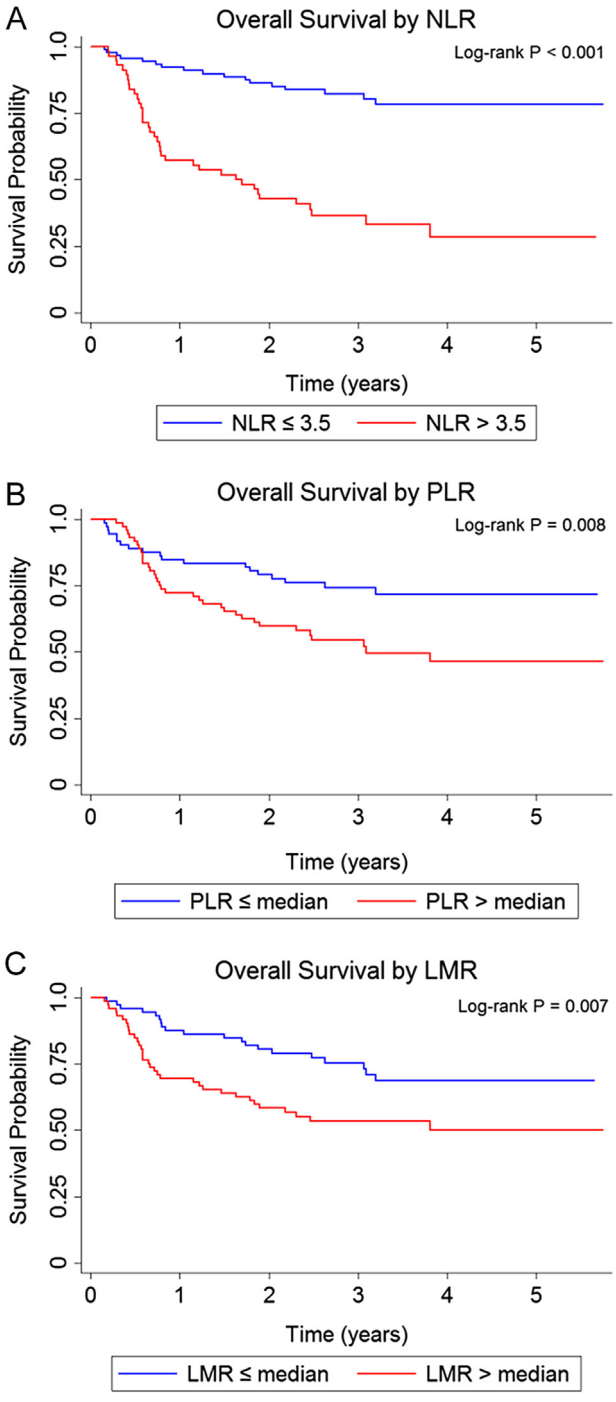

Fig. 1. Kaplan–Meier curves of overall survival by the inflammatory markers. (A) NLR, neutrophil lymphocyte ratio, (B) PLR, platelet lymphocyte ratio, (C) LMR, lymphocyte monocyte ratio.

3.2. Univariable Survival Analysis

Median follow up of the cohort was 3.5 years. 54 deaths (38%) were observed, with an overall 2-year survival rate of 69%. Cancer-related factors (cancer type, stage and treatment intensity), patient-related factors (performance status), and the GA-derived prognostic scale were prognostic of OS (Table 3). Higher NLR (2-year OS; 43% vs 86%, log-rank $p < .001$), higher PLR (2-year OS; 60% vs 79%, log-rank $p = .008$), and lower LMR (2-year OS; 58% vs 80%, log-rank $p = .007$) were associated with poorer OS (Fig. 1).

3.3. Multivariable Survival Analysis

Table 4 summarizes bivariable analyses between NLR, LMR and PLR and covariates (traditional factors and GA-derived prognostic scale). The association between inflammatory markers and OS was attenuated after adjustment for covariates. NLR remained a significant predictor of OS in both the "traditional model" adjusting for cancer type, stage, age, KPS, and treatment intensity (HR = 2.70, $p = .002$) and the "fully adjusted model" adjusting for cancer type, stage, age, KPS, treatment intensity and GA-derived prognostic scale (HR = 2.16, $p = .025$). PLR and LMR were no longer significant predictors in the multivariable models (Table 5). Interestingly, both NLR (HR 2.16, p = .025, Table 6) and the GA-derived prognostic scale (HR 1.46, $p = .032$) were significant prognostic variables in the "fully adjusted model" while KPS, a commonly used instruments of functional performance, was not significant (HR 1.50, $p = .266$).

3.4. Exploratory Analysis of NLR

We assessed the prognostic value of NLR for cancer-specific survival (CSS). Of 54 deaths, 39 (72%) were attributable to cancer in this dataset. NLR, cancer type, stage, KPS, treatment intensity and GA-derived prognostic scale were prognostic of CSS. In multivariable analysis that included these variables, NLR was significantly related to cancer-specific survival (HR = 2.29, 95% CI; 1.02–5.11, $p = .044$). We also performed a subgroup analysis with 105 patients with non-metastatic disease (stage I-III). HR for NLR in multivariable analysis adjusting for univariable significant variables (cancer type, KPS, treatment intensity and GA-derived prognostic scale) was similar to that for the entire cohort (HR = 2.86, 95% CI; 1.15–7.12, $p = .024$). Finally, we further assessed the prognostic value of NLR independent of GA measures. Among the previously reported prognostic GA measures, ADL (none vs ≥ one limitation), IADL (none vs ≥ one limitation), TUG (TUG; ≤20 vs >20), polypharmacy (prescription drugs ≤3 vs >3), MHI5 (≤80 vs <80) and weight loss in 6 months (<5 vs ≥5%) variables were significantly associated with OS in univariable analysis. Adjusting for these covariates, NLR remained significantly related to OS (HR = 3.29, 95% CI; 1.67–6.47, $p = .001$), as well.

4. Discussion

In our sample of older outpatients with cancer, inflammatory markers NLR, PLR and LMR were prognostic of survival in univariable analyses and NLR remained significant in multivariable analysis. These results are in keeping with previous studies suggesting that ratios of cellular markers of inflammation are associated with survival outcomes in general cancer populations [5–7]. A meta-analysis of 100 studies comprising 40,559 patients with solid tumors demonstrated that higher NLR was associated with a HR for poorer OS of 1.81 (95% CI = 1.67–1.97; $P < .001$) [5]. There is a lack of consensus regarding the most appropriate cut-off for the evaluation of NLR. Previous studies chose their cut-off value on the basis of the median, higher quartile, or values determined by the use of receiver-operating curves [27]. According to the meta-analysis, the median cut-off for high NLR in the included studies was 4.0 (range = 1.9–7.2) for OS [5]. We used the predefined NLR cutoff of 3.5, which is the upper boundary of 95% CI observed in a healthy adult population [27]. NLR > 3.5 was a significant independent predictor of worse survival in our study.

The actual mechanisms of the relationship of high NLR with poor outcomes in older patients with cancer are unclear. Elevated NLR may be due to high neutrophil count, low lymphocyte count, or combination of the two. Compared with differential WBCs in a general (non-cancer) geriatric population ($n = 624$), neutrophil count was numerically higher (mean = 5.20, SD = 2.39 vs mean = 3.97, SD = 1.39) and lymphocyte count was lower (mean = 1.60, SD = 0.67 vs mean = 1.84, SD = 0.62) in our dataset [28]. It is difficult to determine whether elevated NLR is due to the aging process or cancer related. We have shown that high NLR was associated with frailty in older adults with cancer [29]. Frailty is a geriatric syndrome characterized by a decline in physiologic reserve across multiple organ systems and increased vulnerability, leading to adverse health outcomes [30]. Notably, high neutrophil count is correlated with an elevated serum level of IL-6 [31] which is strongly and consistently associated with adverse outcomes in cohort studies of older populations, representing the age-related inflammatory phenotype "inflammageing" [32–35]. Additionally, low lymphocyte count is thought to be a crude marker of immunosenescence, defined as aging-related alterations of the immune system [36, 37]. Elevated NLR may also reflect cancer-related inflammation which can generate tumor-promoting microenvironment. Inflammation facilitates cancer cell

Table 4
Bivariable analysis between the inflammatory markers and the covariates.

Variable		Inflammatory markers								
		NLR			LMR			NLR		
		> 3.5	≤ 3.5	P value	> 3.8 (median)	≤ 3.8	P value	> 170 (median)	≤ 170	P value
No. of patients		56	88		72	72		72	72	
Age, years	≥ 72	29	45	0.939	40	34	0.317	35	39	0.505
	< 72	27	43		32	38		37	33	
Physician-rated KPS	< 80	13	7	0.010*	11	9	0.810*	13	7	0.228*
	≥ 80	43	81		61	63		59	65	
Cancer type	Breast	20	57	0.001	41	26	0.012	31	46	0.012
	Other	36	31		31	46		41	26	
Cancer stage	IV	25	14	< 0.001	26	13	0.015	23	16	0.189
	I - III	31	74		46	59		49	56	
Treatment intensity	Less	11	5	0.014*	11	5	0.184*	12	4	0.061*
	Standard	45	88		61	67		60	68	
GA three-item scale	0	16	49	0.001*	30	35	0.504*	32	33	0.761*
	1	15	26		19	22		19	22	
	2	19	10		17	12		17	12	
	3	6	3		6	3		4	5	

* Fisher's exact test. Abbreviations: KPS, Karnofsky performance status; LMR, lymphocyte monocyte ratio: NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio.

Table 5
Multivariable Survival Analysis.

	Traditional model		Fully adjusted model	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
NLR; > 3.5 vs ≤ 3.5	2.70 (1.43–5.09)	0.002	2.16 (1.10–4.25)	0.025
LMR; > 3.8 (median) vs ≤ 3.8	1.14 (0.63–2.08)	0.661	1.09 (0.60–1.99)	0.779
PLR; > 170 (median) vs ≤ 170	1.18 (0.64–2.18)	0.589	1.06 (0.57–1.98)	0.851

Traditional model is adjusted for cancer type, stage, age, KPS, treatment intensity.
Fully adjusted model is adjusted for cancer type, stage, age, KPS, treatment intensity, and the GA-derived prognostic scale.
Abbreviations: CI, confidence interval; HR, hazard ratio; LMR, lymphocyte monocyte ratio: NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio.

survival and proliferation, promotes angiogenesis and metastasis, and suppresses adaptive immune responses [38]. Neutrophils can secrete vascular endothelial growth factor and hepatocyte growth factor that also stimulate tumor angiogenesis and growth [39, 40]. In addition, lymphocytes are key immune cells in both humoral and cellular antitumor immune responses. Low lymphocyte count is associated with poor survival in patients with cancer [41, 42]. These mechanisms may in part explain the observed association between high NLR and poor outcomes in older adults with cancer.

Our novel finding is that elevated NLR is a significant predictor of worse survival in older adults with cancer not only after adjusting for the traditional prognostic factors, but also adjusting for the GA-derived prognostic scale. Furthermore, NLR was significantly related to OS, independent of the previously reported prognostic GA measures. This observation is in line with a prospective cohort study of 362 community-dwelling older adults wherein high levels of IL-6 (HR = 2.18, 95% CI = 1.29–3.69) and CRP (HR = 2.58, 95% CI = 1.52–4.40) were associated with significantly greater risk of death after adjusting for potential confounders including deficits in the GA domains: functional status, cognition, comorbidity, and social status [14]. Interestingly, in our study, both high NLR and the GA-derived prognostic scale remained significant predictors of OS in the multivariable model. A similar finding has been noted by Rønning et al. in a prospective study of patients aged 70 years or older undergoing elective surgery for colorectal cancer [43]. The authors investigated the predictive value of inflammatory markers and a GA for the development of post-operative complications. Patients were classified as "frail" or "non-frail" based on the GA. Both a high IL-6 (odds ratio (OR) = 2.40, 95% CI = 1.14–5.06) and frail status (OR = 3.06, 95% CI = 1.40–6.69) were significant predictors for severe complications in the multivariable model in a sample of 137 patients. While the explanatory power of inflammatory markers was reduced when the GA variable was included in multivariable models, the inflammation and GA variables remained independently associated with the outcome in our study and Rønning's study. These findings suggest that inflammatory markers may comprise aspects that are not measured in the GA and have predictive value for adverse outcomes in older adults with cancer.

Table 6
Fully adjusted model of NLR.

Variable	HR	95% CI	*P* value
Cellular markers of inflammation			
NLR; > 3.5 vs ≤ 3.5	2.16	1.10–4.25	0.025
Traditional prognostic factors			
Age; ≥ 72 vs < 72	1.39	0.79–2.45	0.255
Physician-rated KPS; < 80 vs ≥ 80	1.50	0.73–3.07	0.266
Cancer type; Breast vs Other	0.17	0.08–0.40	< 0.001
Stage; IV vs I - III	2.04	1.08–3.82	0.027
Treatment intensity; less vs standard	2.18	0.99–4.77	0.052
Geriatric assessment			
Three-item prognostic scale	1.46	1.03–2.05	0.032

Abbreviations: CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; NLR, neutrophil lymphocyte ratio.

There are limitations to our study. First, our cohort was heterogeneous, consisting of older adults with various cancer types and stages. We included these variables as covariates in the multivariable analyses and performed a subgroup analysis of patients with non-metastatic disease (largest subset). Previous studies have reported that inflammatory markers are prognostic of OS in a variety of cancer types and stages [5]. Second, the sample size for this study was small which limits the ability to perform a subgroup analysis by cancer type. A prognostic value of NLR for older adults with cancer could not been fully elucidated in this study. Third, this cohort included only patients seen at a single academic cancer center (NCCH) in the U.S. who were able to speak and read English, and a large proportion of them were non-Hispanic white. These factors may limit the generalizability of our results to the general population of older adults with cancer.

In conclusion, this study evaluated the prognostic value of ratios of cellular markers of inflammation in older adults with cancer and found that NLR > 3.5 was predictive of poorer survival, independent of traditional prognostic factors and a GA-derived prognostic scale. However, we could not develop a new prognostic model based on inflammatory markers and GA items because of small sample size. As NLR and the GA-derived prognostic scale were independently associated with survival, a prognostic scale with both NLR and GA variables may improve prognostic discrimination over GA variables alone. Further investigation in a larger sample with inflammatory markers and GA variables is warranted to develop such a scale and compare its performance to existing tools in geriatric oncology [18, 24] and general geriatrics such as Lee Schonberg Index available in ePrognosis [44–46]. If improved predictive performance is achieved, NLR, a simple and readily available marker in clinical practice, could be easily used as a part of prognostic tool.

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Conflict of Interest

The authors have no conflict of interests

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