

Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis

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Manuscript received August 14, 2013; revised April 3, 2014; accepted April 10, 2014.

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Background Inflammation may play an important role in cancer progression, and a high neutrophil-to-lymphocyte ratio (NLR) has been reported to be a poor prognostic indicator in several malignancies. Here we quantify the prognostic impact of this biomarker and assess its consistency in solid tumors.

Methods A systematic review of electronic databases was conducted to identify publications exploring the association of blood NLR and clinical outcome in solid tumors. Overall survival (OS) was the primary outcome, and cancer-specific survival (CSS), progression-free survival (PFS), and disease-free survival (DFS) were secondary outcomes. Data from studies reporting a hazard ratio and 95% confidence interval (CI) or a *P* value were pooled in a meta-analysis. Pooled hazard ratios were computed and weighted using generic inverse-variance and random-effect modeling. All statistical tests were two-sided.

Results One hundred studies comprising 40 559 patients were included in the analysis, 57 of them published in 2012 or later. Median cutoff for NLR was 4. Overall, NLR greater than the cutoff was associated with a hazard ratio for OS of 1.81 (95% CI = 1.67 to 1.97; *P* < .001), an effect observed in all disease subgroups, sites, and stages. Hazard ratios for NLR greater than the cutoff for CSS, PFS, and DFS were 1.61, 1.63, and 2.27, respectively (all *P* < .001).

Conclusions A high NLR is associated with an adverse OS in many solid tumors. The NLR is a readily available and inexpensive biomarker, and its addition to established prognostic scores for clinical decision making warrants further investigation.

JNCI J Natl Cancer Inst (2014) 106(6): dju124 doi:10.1093/jnci/dju124

The tumor microenvironment and, in particular, the inflammatory response play an important role in cancer development and progression and may be associated with systemic inflammation (1–3). Measurable parameters in blood that reflect the systemic inflammatory response are elevated C-reactive protein, hypoalbuminemia, increased levels of some cytokines, and increased levels of leucocytes and their subtypes (4,5). Biochemical markers of inflammatory response have been incorporated in prognostic scores for several types of cancer (6).

Recently, an elevated ratio of peripheral neutrophils-to-lymphocytes (NLR) has been recognized as a poor prognostic indicator in various cancers (7). However, the consistency and magnitude of the prognostic impact of NLR are unclear. The aim of this study was to use meta-analytic techniques to quantify the prognostic value of peripheral blood NLR on clinical outcome in various solid tumors. We postulated that NLR might be a readily available and inexpensive objective prognostic index that could be used in daily oncologic clinical practice and could help to stratify patients in clinical trials.

Methods

Data Sources and Searches

This analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (8). An electronic search of the following databases was undertaken: Medline (host: OVID) from 1946 to January 2013; EMBASE (host: OVID) from 1974 to January 2013; Cochrane Database of Systematic Reviews from 2005 to November 2012; American Society of Clinical Oncology abstracts 2011 to 2013; and European Society of Medical Oncology abstracts 2011 to 2012. (It was expected that data presented earlier would be captured in full publications.) Search terms included “cancer,” “neutrophils,” “lymphocytes,” and “ratio.” Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. The full search strategy is described in the Supplementary Methods (available online).

Study Selection

Inclusion criteria for the primary analysis were as follows: 1) studies of people with solid tumors reporting on the prognostic impact

of the peripheral blood NLR, and 2) availability of a hazard ratio (HR) and 95% confidence interval (CI) or a *P* value for overall survival (OS). For a secondary analysis, studies providing a hazard ratio for cancer-specific survival (CSS), progression-free survival (PFS), disease-free survival (DFS), or recurrence-free survival (RFS) were included as well. Duplicate publications were excluded. Two reviewers (A. Templeton, M. McNamara) evaluated independently all of the titles identified by the search strategy. The results were then pooled, and all potentially relevant publications were retrieved in full. The same two reviewers then assessed the full articles for eligibility. Inter-reviewer agreement was assessed using Cohen's kappa. Disagreement was resolved by consensus. Corresponding authors were contacted to clarify missing or ambiguous data. To avoid inclusion of duplicated or overlapping data, we compared author names and institutions where patients were recruited and contacted authors to address potential concerns. In cases where no answer was obtained and substantial doubts remained, the study reporting fewer patients was not included in the analysis.

Data Extraction

OS was the primary outcome of interest. CSS, PFS, and DFS were secondary outcomes. Data were collected using predesigned abstraction forms. The following details were extracted: name of first author, type of publication (abstract, full text), year of publication, journal, number of patients included in analysis, disease site, disease stage (nonmetastatic, metastatic, mixed [nonmetastatic and metastatic]), collection of data (prospective, retrospective), cutoff defining high NLR used for peripheral blood NLR, consideration of receiver operating characteristic curves (C-index) for selection of cutoff where available, and hazard ratios and associated 95% confidence intervals for OS, PFS, DFS, or RFS as applicable. Hazard ratios were extracted preferentially from multivariable analyses where available. Otherwise, hazard ratios from univariate analyses were extracted.

Data Synthesis

The meta-analysis was conducted initially for all included studies for each of the endpoints of interest. Subgroup analyses were conducted for predefined parameters such as disease site, disease stage, whether data were derived from univariate or multivariable analyses, and whether data were published in abstract form or as full articles. Disease site subgroups were generated for the main outcome if at least three studies on that site were available; the remaining studies were pooled in a subgroup termed "other."

Statistical Analyses

Extracted data were combined into a meta-analysis using RevMan 5.1 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Estimates of hazard ratios were weighted and pooled using the generic inverse-variance and random-effect model (9). Analyses were conducted for all studies, and differences between the subgroups were assessed using methods described by Deeks et al. (10). Meta-regression analysis was performed to evaluate the effect of NLR cutoff on the hazard ratio for OS. Publication bias was assessed by visual inspection of the funnel plot. Heterogeneity was assessed using Cochran *Q* and *I*² statistics. All statistical tests were two-sided, and statistical significance was defined as *P* less than .05. No correction was made for multiple testing.

Results

Included Studies

One hundred studies with a total of 40 559 patients were included (Figure 1). Cohen's kappa for inter-reviewer agreement was 0.86 (95% CI = 0.81 to 0.89). Characteristics of included studies are shown in Table 1; most (57%) were published in 2012 or later.

Overall Survival

Seventy-nine studies comprising 33 432 patients reported HR for OS. Four studies analyzed NLR as a continuous variable (pooled HR = 1.10; 95% CI = 1.03 to 1.17; *P* = .004) and were excluded from the main analysis. The median cutoff for high NLR was 4.0 (range = 1.9–7.2). Eleven of the eligible 75 studies (15%) reported a non-statistically significant hazard ratio (ie, the 95% confidence intervals crossed 1); a forest plot of all studies is presented as Supplementary Figure 1 (available online). Overall, NLR greater than the cutoff was associated with a hazard ratio for OS of 1.81 (95% CI = 1.67 to 1.97; *P* < .001). The effect of NLR on OS among disease subgroups is shown in Figure 2A. The prognostic effect of NLR was highest in mesothelioma (HR = 2.35; 95% CI = 1.89 to 2.92), followed by pancreatic cancer (HR = 2.27; 95% CI = 1.01 to 5.14), renal cell carcinoma (HR = 2.22; 95% CI = 1.72 to 2.88), colorectal carcinoma (HR = 1.91; 95% CI = 1.53 to 2.39), gastroesophageal cancer (HR = 1.66; 95% CI = 1.46 to 1.88), non-small cell lung cancer (HR = 1.66; 95% CI = 1.40 to 1.96), cholangiocarcinoma (HR = 1.43; 95% CI = 1.25 to 1.63), and hepatocellular carcinoma (HR = 1.43; 95% CI = 1.23 to 1.66). The hazard ratio for the subgroup of other unselected solid tumors was 1.71 (95% CI = 1.52 to 1.92). Differences between disease subgroups were statistically significant (*P* for subgroup difference = .001). For the nine disease-site subgroups analyzed, there was statistically significant heterogeneity among trials of colorectal carcinoma (*P* < .001) and pancreatic cancer (*P* for both < .001), whereas heterogeneity among trials of gastroesophageal cancer (*P* = .26), mesothelioma (*P* = .82), non-small cell lung cancer (*P* = .84), hepatocellular carcinoma (*P* = .11), cholangiocarcinoma (*P* = .76), and other tumors (*P* = .27) was non-statistically significant.

The effect of NLR on OS among different disease stages is shown in Figure 2B. The hazard ratios were 1.57 (95% CI = 1.36 to 1.82) for nonmetastatic disease, 1.80 (95% CI = 1.63 to 1.99) for metastatic disease, and 1.79 (95% CI = 1.63 to 1.97) for a mixed group consisting of studies that included both metastatic and nonmetastatic patients. Although high NLR for subjects with nonmetastatic disease was associated with a numerically lower value for the hazard ratio than for subjects with metastatic cancer, this difference was not statistically significant (*P* for subgroup difference = .12).

Sensitivity analyses are presented in Table 2. Studies with retrospective collection of data tended to report higher hazard ratios compared with studies with prospectively collected data. The scatter plot for the meta-regression is shown in Figure 3. Overall, there was a minor but statistically significant association between NLR cutoff and the hazard ratio for OS (β = 0.012; *P* = .04). There was evidence of publication bias, with fewer small studies reporting negative results than would be expected (Figure 4).

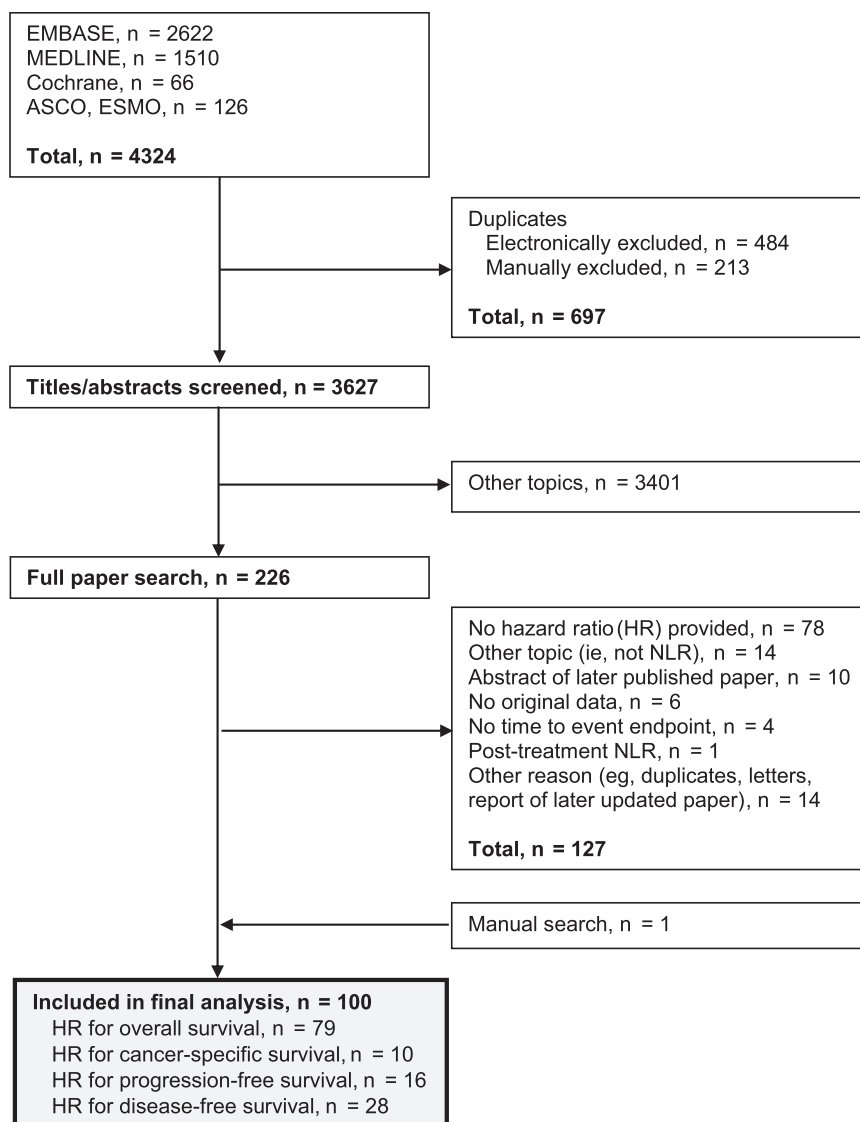


Figure 1. Selection of studies included in the analysis. NLR = neutrophil-to-lymphocyte ratio.

Table 1. Characteristics of included studies*

Characteristics	Studies (n = 100)	Patients (n = 40559)	References
Type of publication, No. (%)			
Full paper	81 (81)	37 154 (92)	(34,39–118)
Conference abstract	19 (19)	3405 (8)	(33,119–135)
Year of publication, No. (%)			
2007–2008	7 (7)	3217 (8)	(54–56,59,78,81,107)
2009–2010	17 (17)	3982 (10)	(39,42,48,51,58,60,68,73,80,84,86,87,95,97,99,101,103)
2011	19 (19)	4614 (11)	(33,40,49,52,62,63,66,69,79,83,96,98, 104,118,121,124,125,131,132)
2012	38 (38)	23840 (59)	(34,43,44,46,47,50,53,57,61,64,65,67,71,72,74–77,88,92– 94,100,102,105,106,109,117,119,120,122,123,126–130,135)
2013	19 (19)	4906 (12)	(41,45,70,82,85,89–91,108,110–116,133,134)
Data collection, No. (%)			
Prospective	26 (26)	6608 (16)	(34,46,49,54,56,60,69,73,81–83,85,86,90,96,99,100,107,109, 110,112,114,127,128,132,135)

(Table continues)

Table 1 (Continued).

Characteristics	Studies (n = 100)	Patients (n = 40559)	References
Retrospective	74 (74)	33951 (84)	(33,39–45,47,48,50–53,55,57–59,61–68,70–72,74–80, 84,87–95,97,98,101–106,108,111,113, 115–126,129–131,133,134)
Reported endpoints, No. (%)			
Overall survival	79 (79)	33432 (82)	(33,34,39,41–46,48–50,53,54,59,61–70,73,74,76–81,83,84, 86,89,90,92–112,114–120,122–128,130–135)
Cancer-specific survival	10 (10)	14407 (36)	(40,52,57,75,78,91,94,113,115,130)
Progression-free survival	16 (16)	7822 (19)	(34,45,47,49,61,65,67,71,77,101,108,111,120,121,124,129)
Disease-free survival	28 (28)	7203 (18)	(43,46,51,55,56,58–60,63,64,66,72,74,79,81, 82,85–88,90,96,104,106,109,110,116,123)
Disease site, No. (%)			
Colorectal carcinoma	22 (22)	8849 (22)	(33,43,47,49,51,55,59,63,67,73,76,78,80–82,86,109,121–123, 125,135)
Gastroesophageal carcinoma	14 (13)	4548 (11)	(52,53,65,66,72,75,83,84,96,97,103,106,107,127)
Hepatocellular carcinoma	11 (11)	1667 (4.1)	(46,56,58,60,62,79,85,90,93,104,114)
Renal cell carcinoma	8 (8)	1704 (4.2)	(45,87–89,112,115,120,124)
Non-small cell lung cancer	7 (7)	1591 (3.9)	(34,44,95,101,102,108,111)
Mesothelioma	7 (7)	693 (1.7)	(68–70,92,131,132,134)
Pancreatic cancer	4 (4)	466 (1.1)	(39,42,99,105)
Multiple sites	3 (3)	12683 (31)	(50,94,98)
Cholangiocarcinoma	3 (3)	973 (2.4)	(54,110,133)
Breast cancer	3 (3)	1195 (2.9)	(41,113,117)
Castration resistant prostate cancer	3 (3)	1073 (2.6)	(71,100,129)
Nasopharyngeal carcinoma	2 (2)	1773 (4.4)	(40,61)
Soft tissue sarcoma	2 (2)	483 (0.5)	(64,116)
Ovarian carcinoma	2 (2)	427 (1.1)	(48,118)
Urothelial carcinoma	2 (2)	393 (1.0)	(57,126)
Cervical cancer	1 (1)	1061 (2.6)	(77)
Gastrointestinal stromal tumor	1 (1)	335 (0.8)	(90)
Hodgkin's lymphoma	1 (1)	312 (0.8)	(74)
Oral carcinoma	1 (1)	97 (0.2)	(91)
Anal carcinoma	1 (1)	92 (0.2)	(130)
Glioblastoma	1 (1)	84 (0.2)	(119)
Carcinoma of unknown primary	1 (1)	60 (0.1)	(128)
Disease stage, No. (%)			
Nonmetastatic	36 (36)	10715 (26)	(40,42,43,46,47,51–54,56–58,60,63,64,72,76,78,79,84,85,87, 88,90,99,102,104,106,113,115,116,119,123,126,130)
Metastatic	28 (28)	7675 (19)	(33,44,45,49,55,59,65,67,71,73,78,81,86,89,98,100,107, 109,111,112,120–122,124,125,127,129,132,135)
Mixed, nonmetastatic and metastatic	36 (36)	22169 (55)	(34,39,41,48,50,61,62,66,68–70,74,75,77,80,82,83,91–97, 101,103,105,108,110,114,117,118,128,131,133,134)
Cutoff for NLR, No. (%)			
Continuous	4 (4)	1547 (3.8)	(34,77,95,99)
<3.0	21 (21)	6627 (16)	(46,48,52,53,57,58,61,80,84,87,88,90, 91,102,107,108,113,114,121,126)
3.0 to <4.0	25 (25)	8701 (21)	(33,40–42,45,47,62,65,66,69–71,98,104,110, 112,115–117,120,124,127,129,132,133)
4.0 to < 5.0	14 (14)	15173 (37)	(51,67,74,83,85,89,94,97,101,118,119,123,130,135)
5.0	33 (33)	8189 (20)	(39,43,44,49,50,54–56,59,60,63,64,68,73,75,76,78,79,81,82, 86,92,93,96,100,103,105,106,109,111,122,128,131)
>5.0	2 (2)	137 (0.3)	(72,134)
Not reported	1 (1)	185 (0.5)	(125)

* Because of rounding, not all percentages total 100. NLR = neutrophil to lymphocyte ratio.

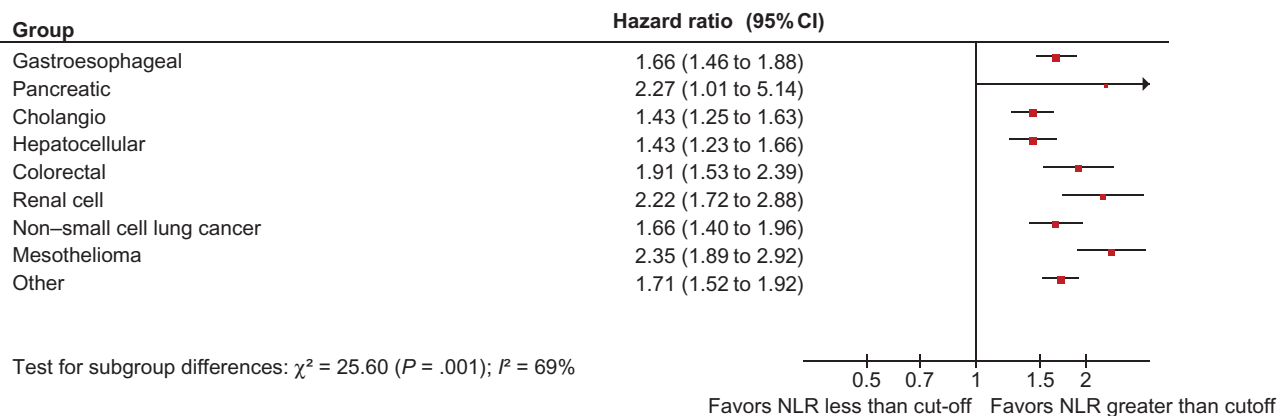
Cancer-Specific Survival

Ten studies comprising 14407 patients reported hazard ratios for CSS. The median cutoff for high NLR was 3.85 (range = 1.9–5.0). Overall, NLR greater than the cutoff was associated with a hazard ratio for CSS of 1.61 (95% CI = 1.36 to 1.91; *P* < .001). There were no statistically significant differences between disease sites (*P* = .26) (see Table 3).

Progression-Free Survival

Sixteen studies comprising 7822 patients reported hazard ratios for PFS. The median cutoff for high NLR was 3.0 (range = 2.0–5.0). Overall, NLR greater than the cutoff was associated with a hazard ratio for PFS of 1.63 (95% CI = 1.39 to 1.91; *P* < .001). There were statistically significant differences between disease sites (*P* = .01) (see Table 3).

A



B

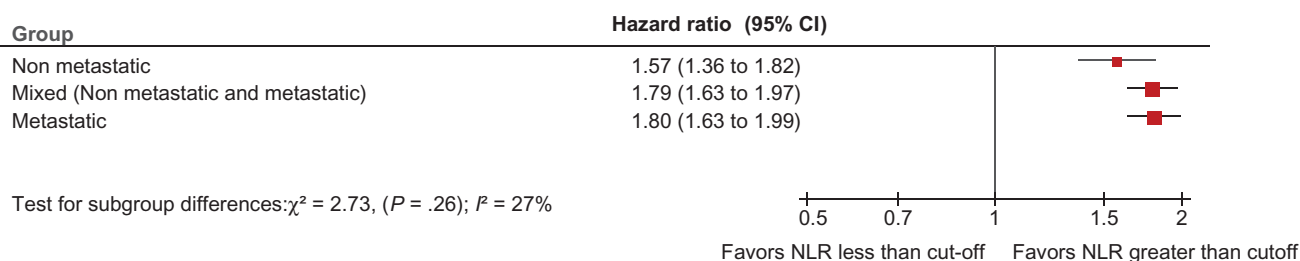


Figure 2. Forest plots showing hazard ratio for overall survival for neutrophil-to-lymphocyte ratio (NLR) greater than or less than the cutoff. **A)** Hazard ratios by disease subgroups. **B)** Hazard ratios by disease stages. Hazard ratios for each study are represented by the **squares**, the **size of the square** represents the weight of the study in the meta-analysis, and the **horizontal line** crossing the square represents the 95% confidence

interval (CI). All statistical tests were two-sided. The subgroup “other” includes one study each of glioblastoma, nasopharyngeal cancer, Hodgkin’s lymphoma, urothelial cancer, cervical cancer, carcinoma of unknown primary, bone metastasis, castration-resistant prostate cancer, and anal carcinoma; two studies each of ovarian cancer, breast cancer, and soft tissue sarcoma; and three studies of various sites.

Table 2. Sensitivity analysis of main outcome*

Subgroup	HR (95% CI)	<i>P</i> for subgroup difference
Type of publication		
Full paper	1.75 (1.62 to 1.89)	.53
Abstract	1.88 (1.52 to 2.32)	
Data collection		
Prospective	1.58 (1.44 to 1.73)	.03
Retrospective	1.88 (1.69 to 2.09)	
Analysis of hazard ratio		
Multivariable	1.80 (1.65 to 1.97)	.84
Univariate	1.78 (1.48 to 2.14)	
C-index considered		
Yes	1.74 (1.44 to 2.11)	.88
No	1.77 (1.64 to 1.91)	
Cutoffs for NLR		
<3.0	1.64 (1.40 to 1.92)	.30
3.0 to <4.0	1.67 (1.49 to 1.87)	
4.0 to < 5.0	1.73 (1.35 to 2.18)	
5.0	1.94 (1.70 to 2.21)	

* Subgroup differences were analyzed as described by Deeks et al. (9). All statistical tests were two-sided. CI = confidence interval; HR = hazard ratio; NLR = neutrophil to lymphocyte ratio.

Disease-Free (Recurrence-Free) Survival

A total of 28 trials comprising 7203 patients reported hazard ratios for DFS. The median cutoff for high NLR was 5.0 (range = 2.0–7.7). Overall, NLR greater than the cutoff was associated with a hazard ratio for the endpoints of 2.27 (95% CI = 1.85 to 2.79; $P < .001$). There were no statistically significant differences between disease sites ($P = .24$) (see Table 3).

Discussion

Many recent studies have suggested that an elevated NLR is associated with poor survival of subjects with cancer. Here we undertook meta-analysis of 100 studies comprising 40 559 patients with solid tumors to assess the prognostic effect of NLR. We found a consistent effect of an elevated NLR on survival (HR = 1.81) among various disease subgroups and across disease stages. Inflammation has been reported to contribute to the development of many cancers and is now included as a hallmark of cancer (11). The magnitude of effect on OS was highest in mesothelioma, where chronic inflammation plays a key role in the pathogenesis as a result of asbestos exposure (12). In addition, there was a trend

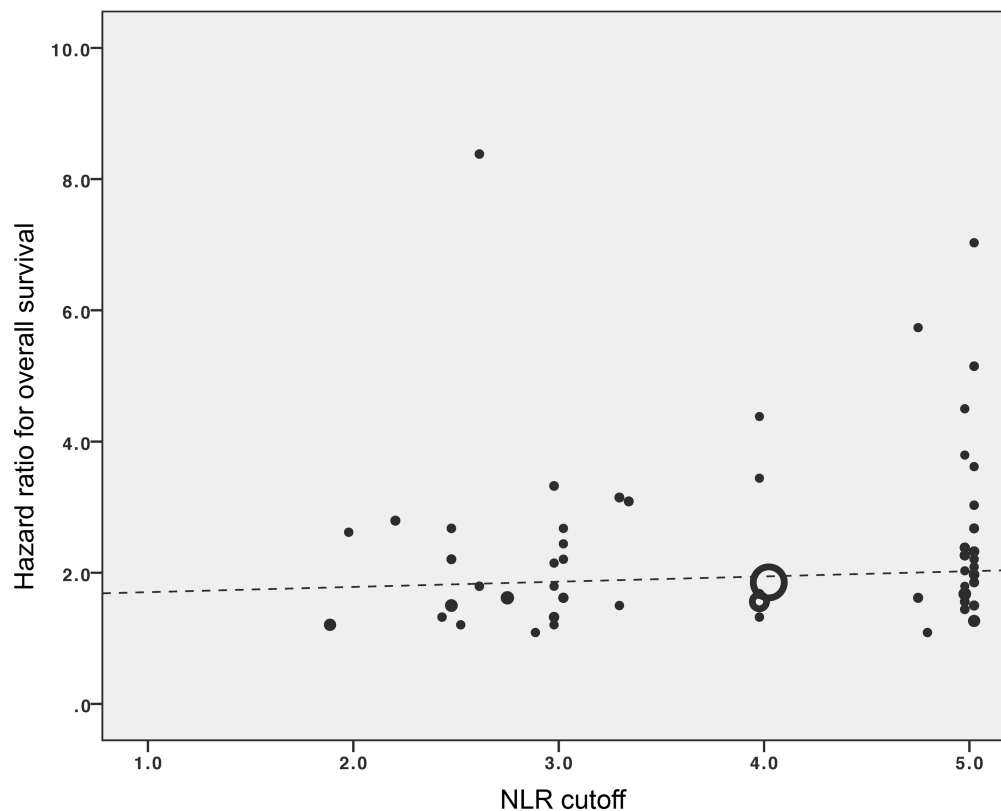


Figure 3. Study-level (ie, at the individual publication level) association of the cutoff used to define neutrophil-to-lymphocyte ratio (NLR) and the hazard ratio for overall survival. Each study is represented by a **circle**, and the **area of the circle** is proportional to the number of patients enrolled in each study. The gradient of the **dashed line** represents the results of the meta-regression ($\beta = 0.012$).

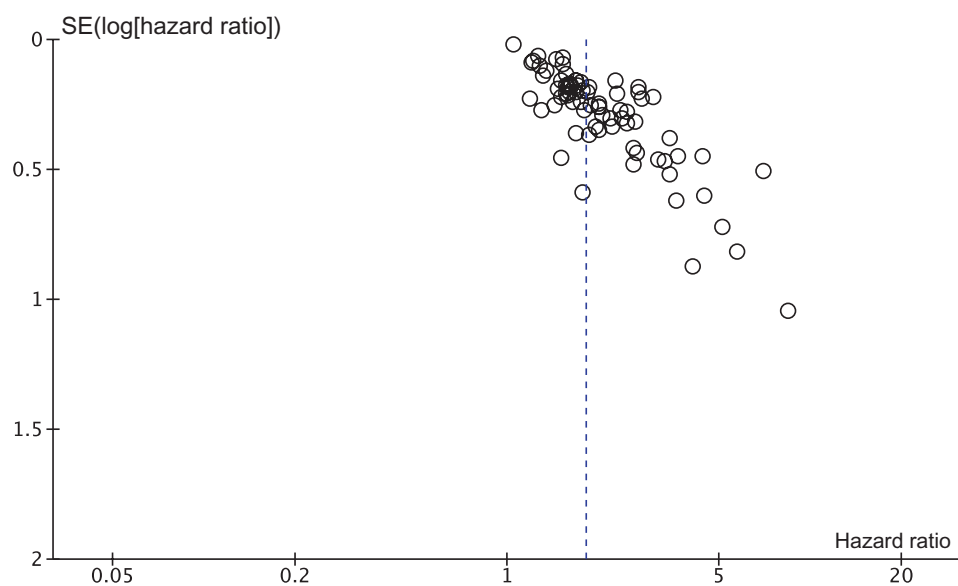


Figure 4. Funnel plot of hazard ratio for overall survival for high neutrophil-to-lymphocyte ratio (**horizontal axis**) and the standard error (SE) for the hazard ratio (**vertical axis**). Each study is represented by one **circle**. The **vertical line** represents the pooled effect estimate.

for the association of high NLR with worse OS to be greater for metastatic than nonmetastatic disease and may reflect either greater tumor burden or a more prolonged chronic inflammatory process (3). The prognostic impact of NLR on CSS, PFS, and DFS (or RFS) was retained across disease sites and stages. Of interest, different cutoffs of NLR for different disease sites

were reported in the included studies, and although some papers reported that cutoffs were determined using receiver operating characteristic curves (C-index), the method of selecting NLR cutoffs remained unclear in many studies. Although there was an association between NLR cutoff and reported hazard ratio for OS, the magnitude of this association was very small and unlikely to

Table 3. Secondary outcomes*

Studies	HR (95% CI)	P for subgroup difference
Cancer-specific survival		
All studies	1.61 (1.36 to 1.91)	
Colorectal carcinoma	1.37 (0.89 to 2.12)	.26
Gastroesophageal carcinoma	1.27 (0.83 to 1.96)	
Other†	1.78 (1.47 to 2.15)	
Progression-free survival		
All studies	1.63 (1.39 to 1.91)	
Colorectal carcinoma	1.32 (1.16 to 1.50)	.01
Non-small cell lung cancer	1.63 (1.33 to 1.99)	
Renal cell carcinoma	1.64 (0.99 to 2.74)	
Other‡	2.08 (1.61 to 2.70)	
Disease-free survival		
All studies	2.27 (1.85 to 2.79)	
Colorectal carcinoma	2.00 (1.53 to 2.62)	.24
Gastroesophageal carcinoma	2.01 (1.51 to 2.69)	
Hepatocellular carcinoma	4.49 (1.87 to 10.8)	
Renal cell carcinoma	2.61 (1.62 to 4.18)	
Other§	1.46 (1.15 to 1.87)	

* CI = confidence interval; HR = hazard ratio.

† Other includes one study of oral cancer, anal carcinoma, breast cancer, and renal cell carcinoma and two studies with various disease sites.

‡ Other includes one study of nasopharyngeal cancer, gastric cancer, and cervical cancer and two studies of castration-resistant prostate cancer.

§ Other includes one study each of Hodgkin's lymphoma, gastrointestinal stromal tumor, and cholangiocarcinoma and two studies of soft tissue sarcoma.

influence the interpretation of our results in view of the relatively narrow range of NLR cutoffs in the included studies.

The mechanisms underlying the association of high NLR and poor outcome of cancer patients are poorly understood. One potential mechanism underlying the prognostic impact of NLR may be an association of high NLR with inflammation. Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells (13,14). The importance of lymphocytes has been highlighted in several studies in which increasing infiltration of tumors with lymphocytes has been associated with better response to cytotoxic treatment and prognosis in cancer patients (15–17). Inflammatory cytokines and chemokines can be produced by both the tumor and associated host cells such as leukocytes and contribute to malignant progression (18). An elevated NLR has been associated with an increase in the peritumoral infiltration of macrophages and an increase in interleukin (IL) 17 (19). Others have reported an association between elevated markers of a systemic inflammatory response with elevated circulating concentrations of several cytokines (IL-1ra, IL-6, IL-7, IL-8, IL-9, IL-12, interferon γ , interferon γ -induced protein 10kDa, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 β , and platelet-derived growth factor, subtype BB) (20). Neutrophils and other cells such as macrophages have been reported to secrete tumor growth promoting factors, including vascular endothelial growth factor (21, 22), hepatocyte growth factor (23), IL-6 (24), IL-8 (25), matrix metalloproteinases (26), and elastases (27), and thus likely contribute to a stimulating tumor microenvironment. Although a variety of cytokines are implicated in the systemic inflammatory response, IL-6 in particular acts to increase

the synthesis of acute-phase proteins, including C-reactive protein, and to decrease albumin production in the liver (28), the two elements encompassed by the Glasgow Prognostic Score, which have been shown to be prognostic in several solid tumors (6). Serum concentrations of IL-6 have been shown to be increased in 13 different cancer types and have been associated with tumor stage and adverse prognosis (29).

Clinicians use prognostic information when speaking to patients. Because NLR provides independent prognostic information, we incorporated NLR in a simple score for men with metastatic castration-resistant prostate cancer (30). In recent years, effort and resources have been invested in the development of biomarkers, which help to tailor therapy for cancer patients. Small studies with cancer patients showed that chemotherapy can normalize elevated NLR early after the introduction of treatment and that patients with normalized NLR may have improved outcome (31,32). Early discontinuation of ineffective treatment and introduction of effective treatment spares unnecessary toxicity and may improve the quality of life of cancer patients. Changes in blood NLR might be useful for tailoring of therapy in patients with advanced cancer where there is a lack of reliable biomarkers. Although the prognostic effect of NLR is smaller in early-stage cancer as compared with advanced cancer, its role might still be relevant for evaluating the early effects of systemic therapy (33–36).

This study had some limitations. Only summarized data rather than individual patient data could be used. Second, we found evidence of publication bias, with fewer small studies reporting negative results than would be expected (Figure 4). Furthermore, we only included studies reporting hazard ratios, and consequently 78 publications reporting on the prognostic value of NLR were excluded (eg, because only odds ratios for death, recurrence, or progression were reported, possibly introducing further selection bias). Among the included studies, nine only reported univariate hazard ratios, which could introduce a bias toward overestimation of the prognostic role of NLR. In some studies, hazard ratios from multivariable analysis may not have been statistically significant: this might be because of inclusion in the multivariable model of other markers of systemic inflammation such as C-reactive protein, hypoalbuminemia, Glasgow prognostic score (6), or platelet-to-lymphocyte ratio (4), which may provide similar information to NLR and thus lead to a non-statistically significant outcome in multivariable analysis. We aimed to address such confounding by performing sensitivity analyses and did not find a statistically significant difference among subgroups. Finally, neutrophil and lymphocyte counts are nonspecific parameters, which may be influenced by concurrent conditions such as infections, inflammation, and medications. NLR also appears prognostic in noncancer conditions [e.g., acute pancreatitis (37) or cardiac events (38)]. Most of the included studies did not explicitly control for such concurrent conditions, and these may confound the measurement of NLR. However, most studies reported NLR before surgery or before start of systemic therapy. It is common for surgery or cytotoxic therapy to be delayed in the setting of active infection; therefore, it is unlikely that NLR would have been influenced by infection in many cases. Despite this, the confounding effect of concurrent inflammatory conditions cannot be completely excluded.

In summary, a high NLR is associated with adverse survival in many solid tumors, and NLR may serve as a cost-effective prognostic biomarker. The evaluation of the utility of NLR measurement for therapeutic decision making is also warranted.

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Funding

AJT's work was supported by a personal grant from the Swiss Cancer Research Foundation. The Swiss Cancer Research Foundation was not involved in planning, conducting, analysis, presentation, and decision to publish this work.

Notes

The authors thank Junhui Zhang from the Princess Margaret Library for running the literature searches.

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