

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

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Abstract

Background: Inflammation influences cancer development and progression. An elevated platelet to lymphocyte ratio (PLR), a marker of inflammation, has been linked to poor prognosis in several malignancies. Here, we quantify the prognostic impact of this biomarker.

Methods: A systematic review of databases was conducted to identify publications exploring the association of blood PLR and overall survival (OS) in solid tumors. Data were pooled in a meta-analysis. Pooled HRs for OS by disease group and by PLR cutoff groups were computed and weighted using generic inverse-variance and random-effect modeling.

Results: Twenty studies comprising 12,754 patients were assessed. Cutoffs for PLR defining risk groups ranged from 150 to 300 and were dichotomous (12 studies; group 1) or split into three groups (<150/150–300/>300, 8 studies; group 2). Higher PLR was associated with significantly worse OS in group 1 [HR = 1.87; 95% confidence interval (CI), 1.49–2.34; $P < 0.001$] and with a nonsignificant association in group 2 (HR per higher category = 1.21; 95% CI, 0.97–1.50; $P = 0.10$). The size of effect of PLR on OS was greater for metastatic disease (HR_[group 1] = 2.0; 95% CI, 1.6–2.7; HR_[group 2] = 1.6; 95% CI, 1.1–2.4) than for early-stage disease (HR_[group 1] = 1.5; 95% CI, 1.0–2.2; HR_[group 2] = 1.0; 95% CI, 0.8–1.3). A significant association was observed for colorectal, hepatocellular, gastroesophageal, ovarian, and pancreatic carcinoma in group 1 and for colorectal cancers in group 2.

Conclusion: A high PLR is associated with worse OS in various solid tumors. Further research of its regulation and relevance in daily practice is warranted.

Impact: PLR is a readily available and inexpensive biomarker with independent prognostic value in solid tumors. *Cancer Epidemiol Biomarkers Prev*; 23(7); 1204–12. ©2014 AACR.

Introduction

Inflammation is a hallmark of cancer (1) and there is often a complex host–tumor relationship with most tumors having inflammatory cells and mediators present in their microenvironment (2, 3). A variety of oncogenes, tumor-secreted factors, and cytokines secreted by inflammatory cells can lead to the recruitment of inflammatory mediators (3). On the basis of these findings, a variety of markers of inflammation have been investigated for association with cancer progression and prognosis (4).

White cell and neutrophil counts, elevated C-reactive protein (CRP), and hypoalbuminemia are the biochemical parameters associated with a systemic inflammatory response that are evaluated most often (4). Several of these parameters have been converted to ratios or prognostic scores such as the Glasgow Prognostic Score (GPS, incorporating CRP and albumin; ref. 5) or the neutrophil to lymphocyte ratio (NLR; ref. 6). Platelets are also part of the inflammatory response and thrombocytosis is common in patients with solid tumors (7, 8). Platelets are known to interact with tumor cells directly and to contain factors that contribute to tumor growth, invasion, and angiogenesis (9). Platelets can protect tumor cells from natural killer cell-mediated lysis, thereby facilitating metastasis (10). The link between thrombocytosis, poor prognosis, and shorter survival time has been established in several types of solid tumors including breast, lung, colon, gastric, and ovarian cancer (11). This is thought to occur due to thrombopoietic cytokines such as interleukin-6 (IL6) being secreted by tumor cells (11). With the recognition that low lymphocyte counts may also be associated with shorter survival (12), the platelet to lymphocyte ratio (PLR) has been studied as a prognostic biomarker. It has been hypothesized that an increased PLR is indicative

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of an increased host inflammatory response associated with more aggressive tumor characteristics (13).

The aim of the present study was to review the literature investigating the association of peripheral blood PLR in solid tumors with overall survival (OS) and to combine the results in a meta-analysis. Our hypothesis was that high PLR correlates with worse OS and may thus serve as a readily available and inexpensive prognostic marker in both clinical practice and for the stratification of patients in clinical trials.

Materials and Methods

This analysis was conducted in line with guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (14).

Data sources and searches

An electronic search of the following databases was undertaken: Medline (host: OVID) from 1946 to June 2013, EMBASE (host: OVID) from 1974 to June 2013, Cochrane Database of Systematic Reviews from 2005 to June 2013. Manual searches were undertaken for abstracts presented at meetings of the American Society of Clinical Oncology from 2011 to 2013, and the European Society of Medical Oncology from 2011 and 2012 (it was assumed that abstracts presented earlier would be captured as fully published papers). Search terms included cancer, platelets, lymphocytes, and ratio. Citation lists of retrieved articles were screened to ensure sensitivity of the search strategy. The full search strategies are described in Supplementary Materials, available online.

Study selection

Inclusion criteria were: (i) studies in solid tumors reporting the prognostic impact of the peripheral blood PLR, (ii) assessment of PLR by cutoff into different risk strata, and (iii) availability of a HR for OS or Kaplan–Meier survival curves from which it could be calculated. Duplicate publications were excluded and for the main analysis so were studies that reported PLR as a continuous variable. Two reviewers (A.J. Templeton and M.G. McNamara) evaluated independently all the titles identified by the search strategy. Inter-reviewer agreement was assessed using Cohen's kappa. Disagreement was resolved by consensus. The results were then pooled and all potentially relevant publications were retrieved in full and assessed for eligibility. Corresponding authors were contacted to clarify any missing or ambiguous data.

Endpoints of interest

Survival based on high versus low PLR was the primary outcome of interest. In exploratory analyses, we compared the relative prognostic impact of PLR with other markers of inflammation, namely the NLR, CRP, and the GPS or modified Glasgow Prognostic Score (mGPS).

Data extraction

Data were collected using predesigned abstraction forms. The following details were extracted: name of first author, type of publication (abstract or full text), year of publication, journal, number of patients included in study, disease site, disease stage [nonmetastatic, metastatic, or mixed (i.e. nonmetastatic and metastatic)], collection of data (prospective or retrospective), cutoff used to define high peripheral blood PLR, ROC curves considered for selection of cutoff (yes or no), and HR for OS with associated 95% confidence intervals (CI) or *P* value. If information about OS was not available, data for cancer-specific survival (CSS) was captured with the assumption that most deaths would be disease related. HRs were extracted from multivariable analyses where available. Otherwise, HRs from univariable analyses were extracted or estimated from Kaplan–Meier survival curves as described by Parmar and colleagues (15). Whenever available, HRs for survival associated with NLR, CRP, and GPS/mGPS were also collected. To evaluate the relative prognostic impact of PLR with these other markers of inflammation, HRs for subgroups defined by different markers were compared.

Data synthesis and statistical analyses

Study quality was assessed on the basis of control for confounding factors. Specifically, good quality studies were defined as those, which explicitly reported that patients with baseline infectious or inflammatory conditions were excluded from the analysis and where assessment of PLR was undertaken before treatment (surgery, systemic therapy, or radiation). Extracted data were combined into a meta-analysis using RevMan 5.2 analysis software (Cochrane Collaboration). Estimates of HRs were weighted and pooled using the generic inverse variance and random-effect model. Analyses were conducted separately for studies using two groups and for studies using three groups to define high versus low PLR. Subgroup analyses were also conducted on the basis of disease site and disease stage. Statistical heterogeneity was assessed using Cochran's *Q* and *I*² statistics. Differences between the reported HR for subgroups defined by different inflammatory markers reported in individual studies were also assessed. Sensitivity analyses were performed using methods described by Deeks and colleagues (16). Publication bias was assessed with visual inspection of funnel plots. Meta-regression analysis was performed to evaluate the effect of study quality on the HR for OS. All statistical tests were two sided, and statistical significance was defined as *P* < 0.05. No correction was made for multiple testing.

Results

Included studies

A total of 22 studies were identified (Fig. 1). Cohen's kappa for inter-reviewer agreement for paper selection was 0.78 (95% CI, 0.63–0.88). Studies included a total of 12,890 patients and characteristics of the studies are

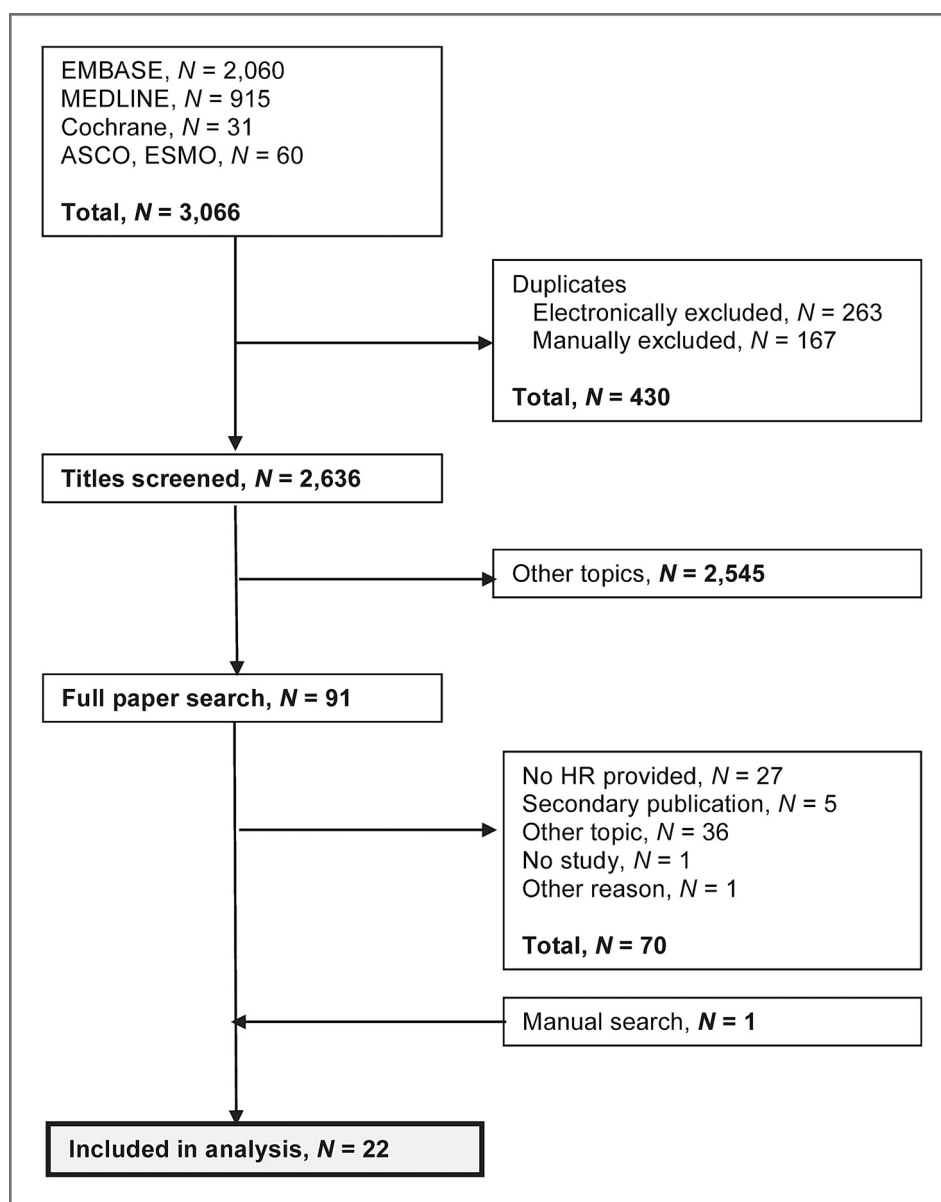


Figure 1. Selection of studies for analysis.

shown in Table 1. Most studies (59%) were published in 2012 or later. Of the 22 identified studies, 19 reported HR for OS and three for CSS. Two studies analyzed PLR as a continuous variable, twelve studies used a dichotomous cutoff for PLR (group 1), and eight defined three risk categories (group 2). All studies utilizing three risk categories reported a single HR, reflecting the average effect of comparing intermediate versus low and high versus intermediate risk (i.e., an increase of one risk category). After exclusion of the two studies analyzing PLR as a continuous variable (pooled HR for OS 1.01; 95% CI, 1.00–1.01; $P < 0.001$), the main analysis was conducted using data from 20 studies comprising 12,754 patients. Inspection of the funnel plots did not reveal any evidence of publication bias (Supplementary Fig. S1, available online).

Overall survival

Overall, higher PLR was associated with worse survival. Among studies of group 1 (median cutoff for PLR = 185), the pooled HR for survival for PLR above the cutoff was 1.87 (95% CI, 1.49–2.34; $P < 0.001$; Fig. 2A). For studies of group 2 (i.e., two cutoffs defining low, intermediate, and high PLR, usually <150, 150–300, >300), HR for OS per risk category was 1.21 (95% CI, 0.97–1.50; $P = 0.10$; Fig. 2B). There was statistically significant heterogeneity in both groups (group 1: Cochran Q, $P < 0.001$, $I^2 = 65\%$; group 2: Cochran Q, $P < 0.001$, $I^2 = 75\%$). In group 1, heterogeneity was introduced by one outlying study with HR = 4.81 (17); exclusion of this study reduced I^2 to 11% ($P = 0.34$) and changed the pooled estimate to 1.70 (95% CI, 1.47–1.95; $P < 0.001$). For group 2, no individual study could explain heterogeneity.

Table 1. Characteristics of included studies

Reference	Disease	Stage	PLR collected pretreatment	Patients with infection and/or inflammatory conditions excluded	N	Cutoff	Outcome
Aliustaoglu et al. (29)	Gastric	Nonmetastatic	Yes	Yes	168	160	OS
Asher et al. (30)	Ovarian	Nonmetastatic and metastatic	Yes	Yes	235	300	OS
Azab et al. (18)	Breast	Nonmetastatic and metastatic	Yes	Yes	437	185 ^a	OS
Bhatti et al. (31)	Pancreatic	Nonmetastatic	Yes	Yes	84	<100/100-200/>200	OS
Caruthers et al. (32)	Rectal	Nonmetastatic	Yes	nr	115	160	OS
Cordiner et al. (33)	Breast	Nonmetastatic	nr	nr	707	nr ^b	CSS
Dutta et al. (34)	Esophageal	Nonmetastatic	Yes	Yes	112	<150/150-300/>300	CSS
Dutta et al. (35)	Gastric	Nonmetastatic	Yes	Yes	120	<150/150-300/>300	CSS
Fox et al. (36)	Renal	Nonmetastatic and metastatic	Yes	nr	362	195	OS
He et al. (37)	Colorectal	Metastatic	Yes	Yes	243	150 ^c	OS
Kinoshita et al. (17)	Hepatocellular	Nonmetastatic and metastatic	Yes	Yes	150	150	OS
Kwon et al. (13)	Colorectal	Nonmetastatic and metastatic	Yes	Yes	200	<150/150-300/>300	OS
Lee et al. (38)	Colorectal	Metastatic	Yes	nr	60	<150/150-300/>300	OS
Pinato et al. (39)	Hepatocellular	Non-metastatic and Metastatic	Yes ^d	Yes	112	300	OS
Pinato et al. (40)	Mesothelioma	Nonmetastatic and metastatic	Yes ^d	Yes	171	300	OS
Proctor et al. (41)	Various	Nonmetastatic	No ^e	No	8,759	<150/150-300/>300	OS
Raungkaewmanee et al. (42)	Ovarian	Nonmetastatic and metastatic	Yes	Yes	166	200	OS
Sakka et al. (43)	Pancreatic/periampullary neuroendocrine	Nonmetastatic	Yes	nr	32	Continuous	OS
Smith et al. (44)	Ampullary	Nonmetastatic	Yes	nr	52	160	OS
Smith et al. (45)	Pancreatic	Nonmetastatic	Yes	nr	104	Continuous	OS
Wang et al. (46)	Gastric	Nonmetastatic	Yes	nr	324	<150/150-300/>300	OS
Wang et al. (47)	Pancreatic	Nonmetastatic and metastatic	Yes	Yes	177	<150/150-300/>300	OS

Abbreviation: nr, not reported.

^aFourth quartile versus others.^bConsidered dichotomous.^c150 versus 150-300.^dD.J. Pinato; personal communication.^eWithin 2 years following diagnosis of cancer.

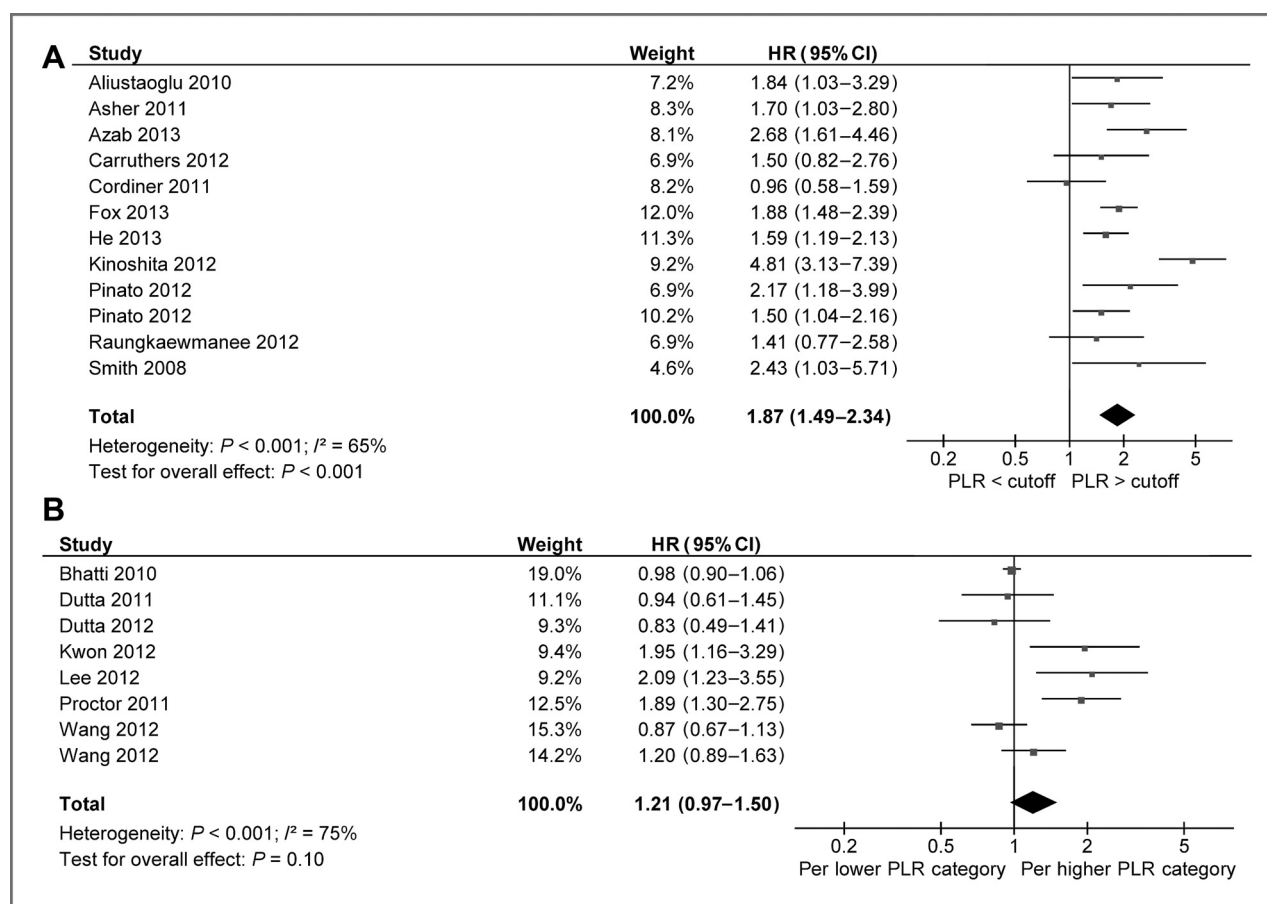


Figure 2. Main analysis of included studies. A, group 1, dichotomized cutoffs for PLR. B, group 2, two cutoffs for PLR.

High PLR was associated with significantly worse survival for colorectal, gastroesophageal, hepatocellular, pancreatic, and ovarian cancers in group 1 (HRs = 1.57, 1.84, 3.33, 2.43, 1.57, respectively) but not for breast cancer (Fig. 3A). For group 2, PLR was associated with worse survival only for colorectal cancer (HR = 2.02) but not for other disease sites (Fig. 3B).

Overall, a prognostic role of PLR was observed for metastatic or mixed groups of patients (HR 2.03; 95% CI, 1.55–2.65; $P = 0.001$ and HR = 1.61; 95% CI, 1.10–2.37; $P = 0.01$ for group 1 and group 2, respectively) but only for patients with nonmetastatic disease when a dichotomous cutoff was used (HR = 1.48; 95% CI, 1.01–2.17; $P = 0.04$ and HR = 1.04; 95% CI, 0.82–1.32; $P = 0.73$ for group 1 and group 2, respectively).

In sensitivity analyses, higher values of HR were reported in full papers as compared with abstracts in group 1, but not in group 2. Further subgroup comparisons and sensitivity analyses are shown in Table 2. The scatter plot for the meta-regression is shown in Supplementary Fig. S2, available online. Overall, studies with good quality reported higher HR for OS than those for poor quality studies. This effect was observed both for studies reporting dichotomous risk groups ($\beta = 0.537$, $P <$

0.001) and for those reporting three risk groups ($\beta = 0.147$, $P = 0.001$).

Comparison with other inflammatory markers

The pooled HRs for PLR compared with other markers of inflammation, namely NLR, CRP, and GPS/mGPS were not statistically different (Table 3). Only two studies reported HRs for NLR and PLR from multivariable analyses. In one of these studies (18), both NLR and PLR retained statistical significance. In the second study, NLR was not independently prognostic after adjustment for PLR.

Discussion

Several studies have considered the relationship between inflammatory markers and outcome of patients with solid tumors. Here, we used meta-analysis to combine twenty studies exploring the prognostic role of PLR in 12,754 patients with solid tumors. Most of these studies have been published since 2012, highlighting the recent interest in PLR as a potential prognostic marker. We found an association between elevated PLR and poor survival. In studies reporting a dichotomous cutoff for PLR, this association was seen among several disease sites and both

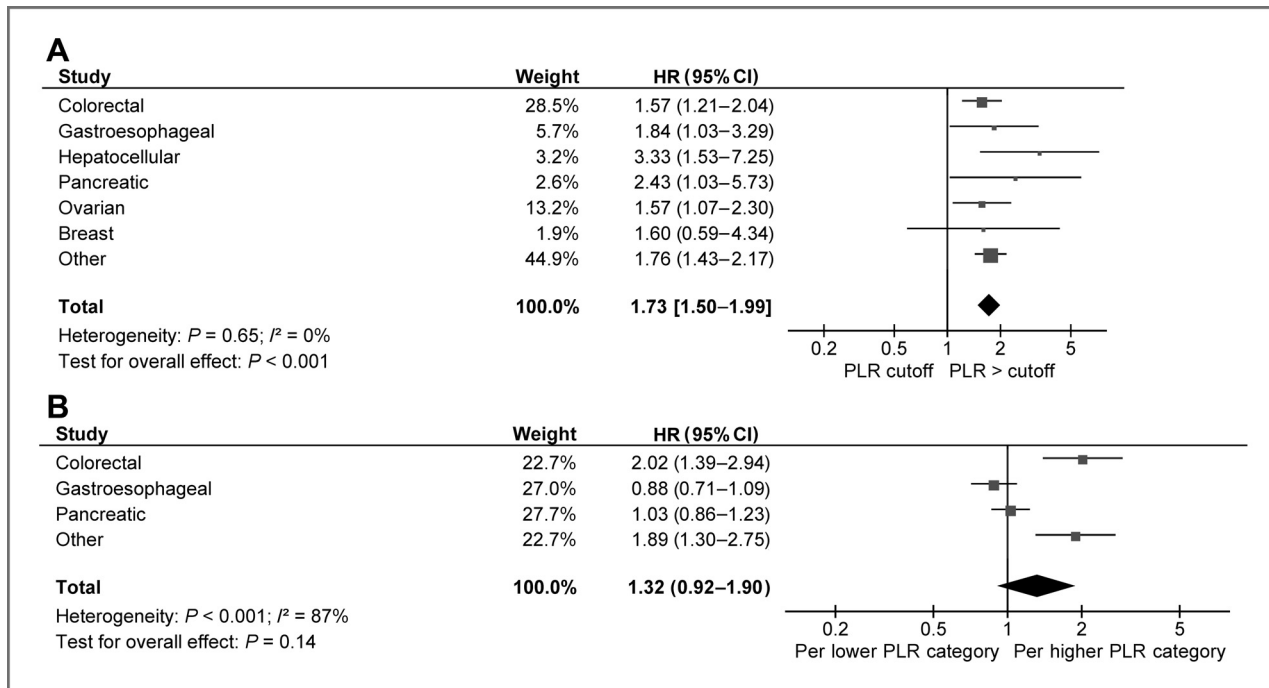


Figure 3. Prognostic impact of PLR according to disease sites. A, group 1, dichotomized cutoffs for PLR. B, group 2, two cutoffs for PLR.

for metastatic and nonmetastatic disease, whereas it was less apparent for studies reporting three risk categories defined by two different cutoffs for PLR. Presumably, this at least in part is due to numerically lower HRs that apply

per higher risk category compared with use of single cutoffs. As the direction of effect is the same, it may be hypothesized that if binary cutoffs had been used in studies reporting three risk groups, these may have

Table 2. Subgroup and sensitivity analyses

	Group 1 (dichotomous cutoff)				Group 2 (three categories)			
	N	HR (95% CI)	P^a	P^b	N	HR (95% CI)	P^a	P^b
Disease stage								
Nonmetastatic	4	1.48 (1.01–2.17)	0.04		5	1.04 (0.82–1.32)	0.73	
Metastatic/mixed	8	2.03 (1.55–2.65)	<0.01	0.19	3	1.61 (1.10–2.37)	0.01	0.06
Article type								
Abstract	1	0.96 (0.58–1.59)	0.87		1	2.09 (1.23–3.55)	0.01	
Full paper	11	1.98 (1.60–2.46)	<0.01	0.01	7	1.13 (0.92–1.40)	0.25	0.04
Study type								
Prospective	3	1.78 (1.49–2.14)	<0.01		1	1.95 (1.16–3.29)	0.01	
Retrospective	9	1.88 (1.35–2.61)	<0.01	0.79	7	1.14 (0.92–1.42)	0.23	0.06
Variable type								
Multivariable	3	1.90 (1.31–2.75)	<0.01		3	1.95 (1.50–2.55)	<0.01	
Univariable	9	1.87 (1.41–2.47)	<0.01	0.95	5	0.98 (0.91–1.05)	0.54	<0.01
HR								
Reported in study	8	1.67 (1.38–2.04)	<0.01		8	1.21 (0.97–1.50)	0.10	
Estimated from survival curves	4	2.41 (1.33–4.38)	<0.01	0.25	0			NA
ROC curve								
Considered	2	2.65 (0.80–8.83)	0.11		1	1.89 (1.30–2.75)	<0.01	
Not considered	10	1.71 (1.47–1.99)	<0.01	0.48	7	1.11 (0.91–1.36)	0.30	0.02

^a P value for HR.

^b P value for subgroup difference.

Table 3. Comparison of relative risk of HR between PLR, CRP, and GPS (group 1 only)

	Studies (N)	Pooled HR for PLR (95% CI)	Pooled HR for comparator (95% CI)	Subgroup difference
PLR vs. NLR (multivariable ^a)	2	2.13 (1.36–3.33)	1.76 (0.44–7.13)	0.800
PLR vs. NLR (univariable ^a)	7	1.76 (1.42–2.18)	2.20 (1.52–3.20)	0.310
PLR vs. CRP (univariable ^a)	2	1.66 (1.20–2.29)	1.96 (1.43–2.68)	0.470
PLR vs. GPS/mGPS (univariable ^a)	2	1.66 (1.20–2.29)	2.14 (1.55–2.95)	0.280

^aHR derived from univariable and multivariable models, respectively.

reached statistically significance. Sensitivity analyses of type of publication and data collection did not change the overall result.

Differences in HRs were observed between cancer sites and may be the result of inflammation playing differing roles in different types of cancer. For example, strong links with systemic inflammation and elevated inflammatory markers (CRP and GPS) have been established in colorectal cancer (4). In the present analysis, this is supported by a strong association between PLR and OS for this disease. In ovarian cancer, where we found a HR of 1.57, both thrombocytosis and elevated inflammatory markers have been linked to poor prognosis (4, 8).

The mechanisms underlying the association of high PLR and poor outcome of patients with cancer are poorly understood. Inflammatory cytokines and chemokines can be produced by both the tumor and associated host cells such as leukocytes and platelets, contributing to malignant progression (19). Indeed, we found the strongest association between PLR and survival in metastatic or mixed groups of patients when compared with study populations with locoregional disease. Although a variety of cytokines are implicated in the systemic inflammatory response, IL6 acts to increase the synthesis of acute phase proteins, including CRP, and to decrease albumin production in the liver, the two elements encompassed by the GPS (20). IL6 also stimulates the differentiation of megakaryocytes to platelets and is involved in recruitment of neutrophils (21, 22). Several studies have shown that IL6 can stimulate thrombopoietin production and can lead to increases of platelet counts in patients with cancer (23). In patients with ovarian cancer, high IL6 level is an independent predictor of poor prognosis (8). Furthermore, serum concentration of IL6 has been shown to be increased in 13 different cancer types and has been associated with tumor stage and disease progression (22).

In an exploratory analysis, we compared the relative prognostic impact of PLR with other markers of inflammation, namely NLR, CRP, and GPS/mGPS and did not find any of these to be a stronger prognostic marker than the others. In studies reporting HRs for both NLR and PLR, NLR was associated with a numerically higher HR for death in univariable analysis; this may be due to the more varied properties of neutrophils in comparison with

platelets, such as the secretion of various cytokines (24–27), but this difference did not reach statistical significance. Either CRP or GPS/mGPS might be stronger predictors of survival than PLR but data from only two studies were available for comparison. Overall, it is likely that common mechanisms lead to concurrent elevation of multiple inflammatory factors.

Limitations of this study include the fact that only summarized data rather than individual patient data could be used and that two studies were published only in abstract form and have not undergone rigorous peer review. Second, most studies (70%) provided only HRs from univariable analysis which could introduce a bias toward overestimation of the prognostic role of PLR, as HRs in multivariable analysis may have been nonsignificant due to inclusion in the multivariable model of other markers of systemic inflammation such as CRP, hypoalbuminemia, GPS, or NLR. We aimed to address such confounding by performing sensitivity analyses and did not find a significant difference between subgroups. Furthermore, studies not reporting HRs or Kaplan–Meier curves were excluded, potentially introducing further bias. Finally, we cannot exclude the possibility that non-malignant factors may have influenced the reported PLR. Authors of most studies included in our analysis explicitly excluded patients with infection and/or inflammatory conditions and some mentioned exclusion of patients with hypothyroidism, hyperthyroidism, temperature >37.2C, or patients on glucocorticoids or nonsteroidal anti-inflammatory drugs. Furthermore, most studies reported that PLR was calculated from blood counts drawn before actual treatment. Our meta-regression suggests that the effect size of PLR on OS was greater in studies with more comprehensive exclusion of nonmalignant causes of inflammation. Therefore, it is possible that our inclusion of studies without robust control for confounders actually diluted the effect of PLR on outcome.

To establish PLR as a prognostic marker, the clinical significance of this indicator must be further validated. The cutoff value must be established in one cohort of patients and tested in another and the number of patients in each group needs to be considered in the statistical analysis (28). With the use of patient level data, the overlap of outcomes between high and low risk of PLR must be considered. The differing results by cancer site and

metastatic compared with locoregional disease reported here suggest that prognosis based on PLR may not be generalizable across differing patient groups.

In summary, this meta-analysis concludes that a high PLR is an independent factor associated with poorer OS in many solid tumors and is comparable with other established hematologic markers of inflammation. As a cost-effective and readily available biomarker, PLR may thus be useful in the clinical setting. Investigation of the addition of PLR to established prognostic scores to stratify patients in clinical trials is warranted. The selection of the most relevant marker of inflammation to indicate prognosis will require head to head comparisons.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: A.J. Templeton, A. Ocana, E. Amir

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.J. Templeton, M.G. McNamara

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.J. Templeton, M.G. McNamara, F.E. Vera-Badillo, T. Hermanns, A. Ocana, E. Amir

Writing, review, and/or revision of the manuscript: A.J. Templeton, O. Ace, M.G. McNamara, M. Al-Mubarak, F.E. Vera-Badillo, T. Hermanns, B. Seruga, A. Ocana, I.F. Tannock, E. Amir

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.J. Templeton, E. Amir

Study supervision: A.J. Templeton, A. Ocana, I.F. Tannock, E. Amir

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