Prognostic Value of PLR in Various Cancers: A Meta-Analysis

Xin Zhou, Yiping Du, Zebo Huang, Jun Xu, Tianzhu Qiu, Jian Wang, Tongshan Wang, Wei Zhu, Ping Liu
Department of Oncology, First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Abstract

Background: Recently, more and more studies investigated the association of inflammation parameters such as the Platelet Lymphocyte Ratio (PLR) and the prognosis of various cancers. However, the prognostic role of PLR in cancer remains controversial.

Methods: We conducted a meta-analysis of published studies to evaluate the prognostic value of PLR in various cancers. In order to investigate the association between PLR and overall survival (OS), the hazard ratio (HR) and its 95% confidence interval (CI) were calculated.

Results: A total of 13964 patients from 26 studies were included in the analysis. The summary results showed that elevated PLR was a negative predictor for OS with HR of 1.60 (95%CI: 1.35–1.90; $P_{\text{heterogeneity}} < 0.001$). Subgroup analysis revealed that increased PLR was a negative prognostic marker in patients with gastric cancer (HR = 1.35, 95%CI: 0.80–2.25, $P_{\text{heterogeneity}} = 0.011$), colorectal cancer (HR = 1.65, 95%CI: 1.33–2.05, $P_{\text{heterogeneity}} = 0.995$), hepatocellular carcinoma (HR = 3.07, 95%CI: 2.04–4.62, $P_{\text{heterogeneity}} = 0.133$), ovarian cancer (HR = 1.57, 95%CI: 1.07–2.31, $P_{\text{heterogeneity}} = 0.641$) and non-small cell lung cancer (NSCLC) (HR = 1.85, 95%CI: 1.42–2.41, $P_{\text{heterogeneity}} = 0.451$) except for pancreatic cancer (HR = 1.00, 95%CI: 0.92–1.09, $P_{\text{heterogeneity}} = 0.388$).

Conclusion: The meta-analysis demonstrated that PLR could act as a significant biomarker in the prognosis of various cancers.

Introduction

For a long time, cancer is one of the leading causes of death and a major public health problem worldwide [1]. In spite of the increased survival rate of cancer patients in the last decades, newer diagnostic methods with improved sensitivity and specificity are necessary for the proper detection and prognosis of cancer [2]. So both clinicians and researchers have made widespread efforts to identify biomarkers that predict progression of the disease, response to treatment, and survival. Nevertheless, currently there are no suitable predictors that can be widely used in clinical settings, and therefore, better predictive biomarkers, especially serum biomarkers for predicting the prognosis of various cancers are urgently needed.

Recently, more and more evidence showed that a systemic inflammatory response could play an important role in the development and progression of cancer [3–6]. It is well known that inflammation is closely related to different stages of tumor development, including initiation, promotion, malignant conversion, invasion and metastasis. Furthermore, inflammation also affects immune surveillance and responses to therapy [7]. Peripheral blood tests at the time of diagnosis or before treatment may reflect inflammatory conditions within the tumor. Fortunately, systemic inflammation can be assessed by means of widely available markers such as C-reactive protein (CRP), albumin, Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) [8]. Among these markers, PLR, a combination of circulating platelet and lymphocyte counts, is a representative index of systemic inflammation. Its prognostic value had been studied in many types of cancers including ovarian cancer [9], colorectal cancer [10] and so on. And now, a series of studies have explored the correlation between PLR and prognosis of various cancers. However, according to their results, the current opinion on the prognostic role of PLR in cancer is still controversial. We therefore conducted this meta-analysis to reveal the prognostic value of PLR in various cancers.

Materials and Methods

Search strategy and study selection

A systematic review of the studies about PLR in predicting the prognosis of various cancers was performed. Studies were...
identified by searching PubMed, Embase and Web of Science databases using the following search terms: PLR, platelet-to-lymphocyte ratio, platelet lymphocyte ratio or platelet-lymphocyte ratio with cancer, neoplasms or tumor and prognosis or outcome. Both free text and MeSH search for keywords were used. The last search was updated in March 12, 2014. The “related information” function was used to broaden the search and all abstracts, full texts and references were reviewed. Study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11].

The search was conducted by two authors (Huang and Du). We read titles and abstracts of all candidate articles. Articles that could not be categorized based on title and abstract alone were retrieved for full-text review. Articles were independently read and checked for inclusion criteria of articles in this study. Any disagreements were resolved through consensus with a third investigator (Zhou).

Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: (a) studied patients with any type of cancer; (b) investigated the association of pre-treatment PLR and overall survival (OS); (c) published as a full paper in English. Studies were excluded based on the following criteria: (a) letters, reviews, case reports or laboratory studies; (b) studies had duplicate data or repeat analysis; (c) lack of key information for further analysis; (d) non-human research.

Data extraction

Two investigators evaluated and extracted the data independently under the guidelines of the Dutch Cochrane Centre proposed by Meta-analysis of Observational Studies in Epidemiology (MOOSE) [12]. For each study, the following information was recorded: first author, year of publication, country of origin, ethnicity, total number of cases, cancer type, stage, treatment strategy, cut-off value, follow ups and HR of PLR for overall survival with its 95% confidence intervals and P value.

Statistical analysis

All the survival results were estimated as the hazard ratio (HR) for each study. If possible, the HR and 95% confidence intervals (95% CI) were obtained directly from each study publication. When the data was not directly reported, a mathematical estimation was done by calculating the necessary data according to the methods published by Parmar et al [13]. Cochran’s Q test and Higgins I-squared statistic were undertaken to evaluate the heterogeneity of pooled results. A p<0.10 for Q-test suggested significant heterogeneity among studies and the random-effects model (DerSimonian-Laird method) was performed to calculate the pooled HRs [14]. Otherwise, the fixed-effects model (Mantel-Haenszel method) was applied [15]. To explore the potential source of heterogeneity among studies, meta-regression was conducted utilizing variables as year of publication, ethnicity, cancer type, analysis method and cutoff value. To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of each individual study using the “metainiti” STATA command. Begg’s funnel plot and the Egger’s linear regression test were conducted to examine publication bias of literatures and a p<0.05 was considered significant. All statistical analyses were performed with STATA software version 12.0 (STATA Corporation, College Station, TX, USA). And all P values were two-sided.

Results

By the initial search, 630 potentially relevant articles were identified. Then 519 articles were excluded because of obvious lack of relevance. After carefully reading the articles, 95 were excluded (review, letter, non-english studies and studies lack of some data or key information). Finally, 26 articles [9,10,16–39] were included in this meta-analysis (Figure 1). Authors identified 26 potential studies for full-text review, with excellent agreement between authors. The main features of eligible studies are summarized in Table 1. Among them, participants in ten studies were Asian and in the other twelve were Caucasian. A variety of cancers were recorded in our study, including digestive duct cancer, hepaticcellular carcinoma, pancreatic cancer, female reproductive system cancer and non-small cell lung cancer (NSCLC). The cut-off values applied in the studies were not consistent ranging from 100 to 300. Nine studies had a PLR cutoff value of 160 or less, while ten studies used a PLR greater than 160. The remaining seven studies had triple subsets of PLR cutoff, six used 150/300 and one used 100/200. HRs with their 95%CIs were extracted from the graphical survival plots in 4 studies and reported directly in 22 studies, 16 of which calculated HRs by the multivariate analysis and 10 via univariable analysis.

The main results of this meta-analysis are listed in Table 2. It is found that elevated PLR predicted a worse outcome for OS with the combined HR of 1.60 (95% CI: 1.35–1.90, PHeterogeneity < 0.001; Figure 2). Subgroup analyses by ethnicity revealed that negative predictor of PLR for OS was found both in Asian cases (HR = 1.68, 95%CI: 1.28–2.11, PHeterogeneity < 0.001) and in Caucasian populations (HR = 1.55, 95%CI: 1.24–1.95, PHeterogeneity < 0.001). When different cancer types were considered, PLR was a negative prognostic marker in patients diagnosed with gastric cancer (HR = 1.35, 95%CI: 0.80–2.25, PHeterogeneity = 0.011), colorectal cancer (HR = 1.65, 95%CI: 1.33–2.05, PHeterogeneity = 0.995), hepatocellular carcinoma (HR = 3.07, 95% CI: 2.04–4.62, PHeterogeneity = 0.133), ovarian cancer (HR = 1.57, 95%CI: 1.07–2.31, PHeterogeneity = 0.641) and non-small cell lung

Figure 1. Methodological flow diagram of the meta-analysis.

doi:10.1371/journal.pone.0101119.g001
### Table 1. Main characteristics of eligible studies.

| Study            | Year | Country | Ethnicity | Number | Cancer          | Treatment                        | Follow-up (month) * | Cut-off |
|------------------|------|---------|-----------|--------|-----------------|----------------------------------|---------------------|---------|
| Smith et al. [16]| 2008 | UK      | Caucasian | 65     | Ampullary Surgery |                                  | 22.5                | 160     |
| Aliustaoglu et al. [17] | 2010 | Turkey | Caucasian | 168 | Gastric Surgery |                                  | NA                  | 160     |
| Bhatti et al. [18] | 2010 | UK     | Caucasian | 84 | Pancreatic Surgery |                                  | NA                  | 100/200 |
| Proctor et al. [19] | 2011 | UK     | Caucasian | 8759 | Mixed | NA | 18 (5163) | 150/300 |
| Asher et al. [9] | 2011 | UK     | Caucasian | 235 | Ovarian Surgery |                                  | NA                  | 300     |
| Wang et al. [20] | 2012 | China | Asian | 324 | Gastric Surgery |                                  | 39.9 (162) | 150/300 |
| Pinato et al. [21] | 2012 | UK     | Caucasian | 171 | MPM | Mix | NA | 300     |
| Kwon et al. [10] | 2012 | Korea | Asian | 200 | Colorectal Surgery |                | 33.6 (39) | 150/300 |
| Wang et al. [22] | 2012 | China | Asian | 177 | Pancreatic Surgery |                                  | 31.33 (132) | 150/300 |
| Sánchez-Lara et al. [23] | 2012 | Mexico | Caucasian | 119 | NSCLC | Chemotherapy | 6 | 150     |
| Carruthers et al. [24] | 2012 | UK | Caucasian | 115 | Rectal | Preoperative chemoradiation | 37.1 (43) | 160     |
| Pinato et al. [25] | 2012 | UK     | Caucasian | 112 | HCC | NA | NA | 300     |
| Kinoshita et al. [25] | 2012 | Japan | Asian | 150 | HCC | M | 18 (73) | 150/300 |
| Raungkaewmanee et al. [27] | 2012 | Thailand | Asian | 166 | Ovarian Surgery |              | 14.7 (50) | 150     |
| Azab et al. [28] | 2013 | Island | Caucasian | 437 | Breast | Mix | NA | 185     |
| He et al. [29] | 2013 | China | Asian | 243 | Colorectal | Chemotherapy | 21.87 (199) | 150/300 |
| Wang et al. [30] | 2013 | China | Asian | 111 | Cervical | Mix | NA | 142.2   |
| Son et al. [31] | 2013 | Korea | Asian | 624 | Colon | Surgery | NA | 300     |
| Fox et al. [32] | 2013 | Australia | Caucasian | 362 | RCC | Mix | NA | 195     |
| Stotz et al. [33] | 2013 | Austria | Caucasian | 371 | Pancreatic | Mix | NA | 150     |
| Lee et al. [34] | 2013 | Korea | Asian | 174 | Gastric | Chemotherapy | 14.9 | 160     |
| Feng et al. [35] | 2013 | China | Asian | 43 | SCCE | Surgery | NA | 150     |
| Mohamed et al. [36] | 2013 | UK | Caucasian | 60 | CUP | Mix | NA | 300     |
| Unal et al. [37] | 2013 | Turkey | Caucasian | 94 | NSCLC | Chemoradiation | NA | 194     |
| Liu et al. [38] | 2013 | China | Asian | 210 | NSCLC | Chemotherapy | 18.6 | 152.6   |
| Szkandera et al. [39] | 2014 | Austria | Caucasian | 372 | Colon | Surgery | 68 | 225     |

CUP: carcinoma of unknown primary; HCC: hepatocellular carcinoma; Mix: mixed treatment including chemotherapy, hormonal therapy, surgery, radiotherapy, and supportive care; MPM: malignant pleural mesothelioma; NA: not available; NR: upper value not reached; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; RFA: radiofrequency ablation; SCCE: small cell carcinoma of the esophagus; TACE: transcatheater arterial chemoembolization.

*The numbers of patients died or lost during the follow up were recorded in parentheses.

doi:10.1371/journal.pone.0101119.t001
cancer (NSCLC) (HR = 1.85, 95% CI: 1.42–2.41, \( P_{\text{heterogeneity}} = 0.431 \)) except for pancreatic cancer (HR = 1.00, 95% CI: 0.92–1.09, \( P_{\text{heterogeneity}} = 0.386 \)). When performing subgroup analyses stratified by analysis method, we found that increased PLR was a negative predictor for OS both by univariable analysis (HR = 1.49, 95% CI: 1.19–1.87, \( P_{\text{heterogeneity}} < 0.001 \)) and multivariable analysis (HR = 1.38, 95% CI: 1.39–2.23, \( P_{\text{heterogeneity}} = 0.845 \)). Considering different cutoff values, PLR was a negative prognostic marker for the data applying \(< or \leq 160 \) (HR = 1.55, 95% CI: 1.25–1.92, \( P_{\text{heterogeneity}} = 0.194 \)) and the data applying \(> 160 \) (HR = 1.76, 95% CI: 1.53–2.02, \( P_{\text{heterogeneity}} = 0.439 \)). These studies used triple subsets of PLR cutoff revealed the similar results (HR = 1.65, 95% CI: 1.18–2.31, \( P_{\text{heterogeneity}} < 0.001 \)).

The results showed that year of publication \( (p = 0.431) \), ethnicity \( (p = 0.782) \), cancer type \( (p = 0.208) \), analysis method \( (p = 0.200) \) and cutoff \( (p = 0.721) \) did not contribute to the source of heterogeneity.

We used the leave-one-out sensitivity analyses by removing one study per time to check if individual study influenced the results. The result pattern was not obviously impacted by any single study (Figure 3). Begg’s funnel plot and the Egger’s linear regression test were performed to assess publication bias. The figure of the funnel plot did not show any evidence of obvious asymmetry \( (p = 0.826) \); Figure 4). Then, the Egger’s test was performed to statistical test and publication bias was not detected either \( (p = 0.576) \).

### Discussion

To date, a variety of predictors have been found and applied in the prognosis of various carcinomas, such as TNM stage, genetic factors, and inflammatory factors. Many inflammatory markers now can be detected in peripheral blood before treatment. Thus, inflammatory marker is a relatively cheap and convenient predictor. Recently, an authoritative article indicated that inflammation with the interaction between various inflammatory cells and extracellular matrix played a crucial role in tumor microenvironment to tumorigenesis [40]. Another study reported that inflammatory cells could release chemicals, notably reactive oxygen species, which were actively mutagenic for nearby cancer cells, accelerating their genetic evolution toward states of heightened malignancy [7]. Additionally, inflammation was evident at the earliest stages of neoplastic progression and was demonstrably capable of fostering the development of incipient...

---

**Figure 2.** Forrest plots of studies evaluating hazard ratios (HRs) of PLR for overall survival.

doi:10.1371/journal.pone.0101119.g002
neoplasias into full-blown cancers in some cases [41, 42]. Based on these above studies, nowadays many studies investigated prognostic value of various inflammation-based factors including Glasgow Prognostic Score (mGPS) [43], Platelet Lymphocyte Ratio (PLR), Neutrophil Lymphocyte Ratio (NLR) [44], Prognostic Index (PI), and Prognostic Nutritional Index (PNI) [45] in cancer patients. However, the prognostic value of these markers remained inconclusive. Our current study mainly aimed to evaluate the

Table 2. Meta-analysis results.

| Outcome Variables | Number of studies | Number of patients | Model   | HR (95% CI)     | \( p_{\text{heterogeneity}} \) |
|-------------------|-------------------|--------------------|---------|----------------|---------------------------------|
| OS ALL            | 26                | 13946              | Random  | 1.60 (1.35, 1.90) | <0.001                          |
| **Cancer type**   |                   |                    |         |                |                                 |
| Colorectal        | 5                 | 1554               | Fixed   | 1.65 (1.33, 2.05) |                      |
| Gastric           | 3                 | 666                | Random  | 1.35 (0.80, 2.25) | 0.011                           |
| HCC               | 2                 | 262                | Fixed   | 3.07 (2.04, 4.62) | 0.133                           |
| NSCLC             | 3                 | 423                | Fixed   | 1.85 (1.42, 2.41) | 0.451                           |
| Pancreatic        | 3                 | 520                | Fixed   | 1.00 (0.92, 1.09) | 0.388                           |
| Ovarian           | 2                 | 401                | Fixed   | 1.57 (1.07, 2.31) | 0.641                           |
| Others            | 8                 | 10120              | Fixed   | 1.88 (1.76, 2.00) | 0.309                           |
| **Ethnicity**     |                   |                    |         |                |                                 |
| Asian             | 11                | 2422               | Random  | 1.68 (1.28, 2.21) | <0.001                          |
| Caucasian         | 15                | 11524              | Random  | 1.55 (1.24, 1.95) | <0.001                          |
| **Analysis method** |                 |                    |         |                |                                 |
| Univariable       | 16                | 11644              | Random  | 1.49 (1.20, 1.85) | <0.001                          |
| Multivariable     | 10                | 2302               | Fixed   | 1.88 (1.59, 2.23) | 0.845                           |
| **Cutoff values** |                   |                    |         |                |                                 |
| \(<\ or\ =\ 160) | 9                 | 1376               | Fixed   | 1.47 (1.24, 1.73) | 0.194                           |
| \(>160)           | 10                | 2633               | Fixed   | 1.76 (1.53, 2.02) | 0.439                           |
| \(150/300)        | 6                 | 9610               | Random  | 1.76 (1.65, 1.88) | <0.001                          |

HCC: hepatocellular carcinoma; OS: overall survival; NSCLC: non-small cell lung cancer.

doi:10.1371/journal.pone.0101119.t002

Figure 3. Effect of individual studies on the pooled HR for PLR and OS of patients.
doi:10.1371/journal.pone.0101119.g003
role of PLR in cancer. To our knowledge, it is the first meta-analysis to investigate the prognostic role of PLR in cancers.

The analysis combined the outcomes of 13946 cancer patients from 26 individual studies, indicating that elevated PLR significantly predicted poor OS. Subgroup analyses revealed that worse OS with high PLR could be found both in Asian populations and Caucasian cases. Additionally, elevated PLR was a significant negative prognostic marker for various cancer types. When differently analysis strategies were considered, PLR had prognostic value for poor outcome by univariable analysis or multivariable analysis. Cut off values of PLR used in the enrolled studies were various. As shown in Table 1, a total of 7 studies used triple subsets of PLR and the other 19 studies devided the data into two groups. To evaluate the effect of different cut off values on the prognostic value of PLR, we performed subgroup analyses by cut off values and found that patients with elevated PLR suffered worse overall survival compared to those with low PLR regardless of the different cut off values. The results might strengthen the possibility that PLR could act as a reliable biomarker in predicting clinical outcomes in the future. However, due to the different types and small number of patients, different cut off values obtained from each study might reduce the sensitivity and specificity of the prognostic value of PLR. Thus, future research including more cancer types and more patients to identify widely accepted cut off values for various cancers is warranted. Meta-regression was performed to investigate the source of heterogeneity. However, none of the variables listed above contributed to the heterogeneity in our meta-analysis. In fact, the presence of heterogeneity may result from many factors, including age distribution, gender, tumor size and so on. More detailed data was needed to assess the heterogeneity in the future meta-regression.

As shown in Table 2, we can easily learn that PLR is related to prognosis in many cancers, such as colorectal cancer, hepatocellular carcinoma and NSCLC; however, the specific mechanism is still incompletely understood. The relationship of poor prognosis and the elevation of platelets, lymphocytes or their ratio may be explained through an inflammatory process caused by cancer cells. Platelets can promote tumor growth by increasing angiogenesis via the cytokine vascular endothelial growth factor (VEGF) [46]. Wiesner et al. [47] reported that the platelet content of VEGF-A in cancer patients was significantly increased compared to healthy controls. Also some proinflammatory cytokines such as IL-1 and IL-6 promote megakaryocyte proliferation resulting in thrombocytosis [48,49]. Thrombocytosis has been considered as a negative prognostic marker in several cancers [50,51]. Meanwhile, platelet aggregation and degranulation along with the consequent release of platelet-derived proangiogenic mediators within the microvasculature of the tumor also could be an important determinant of tumor growth [52]. On the other hand, lymphocytes play a large role in cancer immune-surveillance, which prevent tumor development [53]. Cancer-related inflammation causes suppression of antitumor immunity by recruitment of regulatory T cells and activation of chemokines resulting in tumor growth and metastasis. In breast cancer and melanoma, tumor-infiltrating lymphocytes have been reported as an important prognostic factor, with higher levels associated with better survival [54,55]. In addition, lymphocytopenia has been reported to be associated with poorer survival outcomes in patients with pancreatic cancer and other gastrointestinal malignancies [56,57]. The association of clinicopathological factors and PLR was explored in few studies retrieved in our analysis. Kwon et al. [10] reported that patients with greater PLR showed an increased likelihood of positive lymph node ratio in colorectal cancer. In the study of Asher et al. [9], PLR could reflect residual disease after surgery and status of clinical stage in ovarian cancer which was consistent with the results of Raungkaewmanee et al. [27]. High PLR was also significantly related to bigger size of the tumor and positive status of lymph nodes metastasis in cervical cancer [30]. Azab et al. [28] showed that higher PLR quartiles had significantly higher rates of lymph node involvement, higher rates of metastases, higher AJCC staging and lower hemoglobin in breast cancer patients. Interestingly, Lee [34] found that elevated PLR was frequently observed in female gastric cancer patients who did not accept operation previously and adjuvant chemotherapy. These findings suggest that PLR can be a predictor of the state of some tumors. As mentioned above, thrombocytosis and lymphocytopenia both correlate with the degree of host systemic inflammation that PLR might reflect a novel inflammatory marker incorporating the two hematologic factors [58].

There were several limitations of this study need to be carefully considered. This study was constrained to studies published in English language only. So publication bias cannot be excluded. In addition, heterogeneity among these studies were relatively large that might be caused by different countries, histological type of cancer or/and other factors. In order to reduce the heterogeneity, different cutoff values of PLR or univariable or multivariate regression model have been conducted in our study. Moreover, due to lack of appropriate data, the association of PLR and other important clinical parameters was not explored. Furthermore, most of the patients included in this meta-analysis suffered from digestive system neoplasms. In the future, studies with more types of cancers and larger sample size are needed to present more reliable results.

In conclusion, the meta-analysis firstly shows that an elevated PLR is a negative predictor for survival for various cancers.

Supporting Information
PRISMA checklist  Checklist S1. (DOC)

Author Contributions
Conceived and designed the experiments: XZ YPD ZBH. Performed the experiments: JX TZQ JW. Analyzed the data: TSW WZ. Contributed reagents/materials/analysis tools: PL. Wrote the paper: YPD ZBH.
References

1. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63: 11–30.

2. Paul D, Kumar A, Gajbhiye A, Santra MK, Srikant R (2013) Mass spectrometry proteomics in molecular diagnostics: discovery of cancer biomarkers using tissue culture. Biomed Res Int 2013: 783513.

3. Mantovani A, Alallena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454: 436–444.

4. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357: 539–545.

5. Mantovani A, Romero P, Palacka AK, Marincola FM (2008) Tumour immunity: effector response to tumour and role of the microenvironment. Lancet 371: 771–785.

6. Colotta F, Alallena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 30: 1073–1081.

7. Garlanda C, Sica A, Mantovani A (2010) Immunity, inflammation, and cancer. Cell 140: 885–889.

8. McMillan DC (2009) Systemic inflammation, nutritional status, and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 12: 223–226.

9. Pinato DJ, Mauri FA, Ramakrishnan R, Wahab L, Lloyd T, et al. (2012) Preoperative neutrophil-to-lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol 15: 499–503.

10. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, et al. (2012) Clinical significance of preoperative neutrophil-to-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 17: 216–222.

11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6: e1000100.

12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2088–2092.

13. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6: e1000100.
55. Mahmoud SM, Paish EC, Powe DG, Macmillan RD, Grainge MJ, et al. (2011) Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol 29: 1949–1953.

56. Fogar P, Sperti C, Basso D, Sanzari MC, Greco E, et al. (2006) Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas 32: 22–28.

57. Romano F, Uggeri F, Crippa S, Di Stefano G, Scotti M, et al. (2004) Immunodeficiency in different histotypes of radically operable gastrointestinal cancers. J Exp Clin Cancer Res 23: 195–200.

58. Smith RA, Bosomtew, Ghaneh P, Sutton R, Evans J, et al. (2008) The platelet-lymphocyte ratio improves the predictive value of serum CA19-9 levels in determining patient selection for staging laparoscopy in suspected periampullary cancer. Surgery 143: 658–666.