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Prognostic Value of Platelet to Lymphocyte Ratio in Laryngeal Carcinoma: A Meta-Analysis

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1. Abstract

1.1. Background: Recently, many studies have been conducted to explore prognostic value of platelet to lymphocyte ratio (PLR) for patients with laryngeal carcinoma, while the results remain controversial. A comprehensive literature search for relevant studies was performed in Web of science, Embase, Pubmed and CNKI website, but any meta-analysis of prognostic value of PLR in laryngeal carcinoma was not found. This meta-analysis was designed to evaluate the prognostic value of PLR in laryngeal carcinoma.

1.2. Method: The following databases were systematically searched from 2015 to 2020: Web of science, Embase, Pubmed and CNKI website. HR and corresponding 95% CI or P values were used to evaluate the prognosis. P<0.05 was considered statistically significant. The main outcome was OS, PFS and RFS. The Cochrane Q test and Higgins I2 statistic were used to assess the heterogeneity of the pooled results. Cochran Q test's p value <0.10 or I2>50% was considered as large heterogeneity between studies and random effect model was performed to calculate the pooled HR and 95% CI. In other cases, fixed effects model was adopted. Sensitivity analysis was conducted by removing each study and recalculating the combined HRs. Begg's test was used to evaluate the publication bias.

1.3. Result: A total of ten studies with 2961 patients were included in this meta-analysis, and combined hazard ratio (HR) and 95% confidence intervals (95% CIs) were served as effect measures. Pooled results showed that elevated PLR was associated with poor overall survival (OS) (HR=5.72, 95% CI: 3.83-8.56, P<0.01) and poor recurrence-free survival (RFS) (HR=8.06, 95% CI:5.55-11.70, P<0.01) in laryngeal carcinoma patients. In addition, high PLR was not significantly correlated with progress-free survival(PFS) (HR=22.71, 95% CI: 0.21-2502.48, P>0.05).

1.4. Conclusion: This meta-analysis revealed that elevated PLR was associated with poor prognosis in laryngeal carcinoma.

2. Keywords: Platelet to lymphocyte ratio, Laryngeal carcinoma, Prognosis, Meta-analysis

3. Introduction

Laryngeal cancer remains one of the most common tumors of the respiratory tract. Fortunately, significant advancements have been made over the past decade in the treatment of laryngeal cancer. Although surgery has been the historical mainstay for localized disease and still is an integral part of treatment, nonsurgical options like radiation and systemic therapy have emerged as viable options. In addition, in the metastatic setting, novel agents are showing promise for this patient population [1]. At present, the prognosis of laryngeal cancer mainly depends on the TNM staging system, but the clinical outcomes of laryngeal cancer patients with the same TNM staging are not identical, and the clinical application of biomarkers for laryngeal cancer is very limited. Growing cancer incidence and mortality demands development of accurate biomarkers to perfect detection, diagnosis, prognostication and monitoring [2]. Therefore, it is particularly important to explore biomarkers for predicting prognostic of laryngeal cancer.

Inflammation is a recognized hallmark of cancer that substantially contributes to the development and progression of malignancies. In established cancers, there is increasing evidence for the roles that local immune response and systemic inflammation have in progression of tumors and survival of patients with cancer [3]. Several inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) have been increasingly studied. PLR is considered to be a prognostic predictor of nasopharyngeal carcinoma, non-small cell lung cancer, gastric cancer, liver cancer, bile duct cancer, pancreatic cancer, kidney cancer, etc [4]. To date, some literatures have studied the association between PLR and the prognosis of laryngeal cancer, but the results of these studies remain controversial [5-17]. Any meta-analysis of PLR in predicting

prognosis of laryngeal cancer was not found. Therefore, we performed this meta-analysis to assess the prognostic value of PLR in laryngeal carcinoma.

2. Materials and Methods

2.1. Search Strategy and Selection Criteria

The following databases were systematically searched from 2015 to 2020: Web of science, Embase, Pubmed and CNKI website. The search strategy was based on combination of following terms: "PLR", "platelet to lymphocyte ratio", "platelet-lymphocyte ratio", "platelet lymphocyte ratio", "laryngeal carcinoma", "laryngeal cancer", "laryngeal tumor". Reviews and reference lists in each identified publications were also manually retrieved for additional publications. Two reviewers independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full-text articles of studies that met all selection criteria were retrieved. Inclusion criteria were as follows: ①patients with laryngeal cancer were diagnosed by histopathology; ②Assess the association of PLR and Overall Survival(OS), Progression-Free Survival(PFS), Recurrence-Free Survival (RFS); ③The study provided sufficient information to calculate the hazard ratio (HR) and 95% confidence interval (CI). Exclusion criteria were as follows: ①case reports of letters and summaries of meetings without original data; ②The study did not provide enough data to calculate HR and 95%CI; ③Overlapping or duplicating data; ④Non-human studies.

2.2. Data Extraction and Quality

All data extractions were performed separately by two independent investigators and disagreements were resolved by joint discussion. The following data were recorded for each eligible study: family name of the first author, year of publication, country of study, sample size, mean age, tumor stage, treatment methods, cut-off value of PLR, clinical end point, HR and 95% CI.

2.3. Statistical Analysis

The primary results of this meta-analysis were performed by the Review Manager Version 5.3 software, $P<0.05$ was considered statistically significant. HR and corresponding 95% CI or P values were used to evaluate the prognosis. The main outcome was OS. The Cochrane Q test and Higgins I^2 statistic were used to assess the heterogeneity of the pooled results. Cochran Q test's p value <0.10 or $I^2>50\%$ was considered as large heterogeneity between studies and random effect model was performed to calculate the pooled HR and 95% CI. In other cases, fixed effects model was adopted. Sensitivity analysis was conducted by removing each study and recalculating the combined HRs. Begg's test was used to evaluate the publication bias.

3. Results

3.1. Features of Included Studies

The literature searching progress was showed in (Figure 1). A total of 10 [8-17] eligible studies published between 2015 and 2020 with 2961 patients were identified. The basic characteristics of the original studies were presented in (Table 1). Eight studies [9-10,12-17] were conducted in China, the other studies [8,11] were conducted in Turkey and Japan respectively. Sample sizes ranged from 103 to 477. The prognostic value of PLR for OS was reported or estimated in eight studies [8-15], whereas the prognostic significance of PLR in PFS was only provided in 2 studies [12-13], and in RFS was in 4 studies [14-17]. Surgical resection as initial treatment for laryngeal carcinoma was reported in 5 studies [8,12,15-17]. Mix treatment (Surgery, Radiotherapy, Chemotherapy) were reported in 5 studies [9-11,13-14], respectively. The cut-off values used for PLR in these studies ranged from 103.96 to 149.90. we divided them into two subgroups: ≥112.00 and <112.00. 8 studies included no distant metastasis [8-9,11-12,14-17], 2 studies included distant metastasis [10,13], 9 studies included all stages [8,10-17], and 1 study included only T3-T4 stages [9]. The scores of study quality assessed by Newcastle-Ottawa quality assessment scale ranged from 5 to 8(with a mean of 7). A high value indicated better methodology.

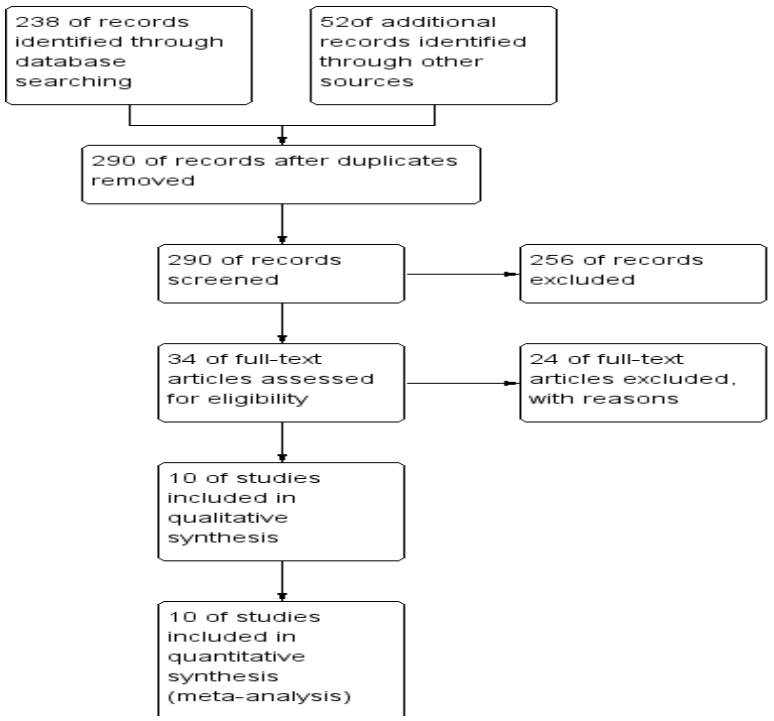

Figure 1: Flow diagram of study selection process

Table 1: Baseline characteristics of all the included studies. OS: overall survival; PFS: progress-free survival; RFS: recurrence-free survival; NOS: Newcastle-Ottawa quality assessment scale.

Author	Year	Country	Sample Size	Mean Age	Treatment	Cut-off Value	Outcome	NOS Score
Medine Kara[8]	2016	Turkey	103	65.01	Surgery	120.32	OS	7
Hu Yanhong[9]	2019	China	286	no reported	Surgery, Radiotherapy	149.90	OS	6
Tao Zhou[10]	2019	China	232	63	Surgery, Radiotherapy, Chemotherapy	116.00	OS	8
Kano,Satoshi[11]	2017	Japan	285	61	Radiotherapy, Chemotherapy	125.00	OS	7
Linyan Chen[12]	2018	China	361	60	Surgery	111.00	OS, PFS	8
Youfang Xun[13]	2019	China	151	65	Radiotherapy, Chemotherapy	106.00	OS, PFS	6
Jie Wang[14]	2016	China	120	60.6	Surgery, Radiotherapy, Chemotherapy	112.00	OS, RFS	8
Bing Chen[15]	2018	China	477	49.1	Surgery	no reported	OS, RFS	8
Huijun Chen[16]	2020	China	473	63	Surgery	103.96	RFS	7
Huijun Chen[17]	2019	China	473	no reported	Surgery	103.96	RFS	5

3.2. Overall Survival Outcomes

The data from all the eight studies [8-15] revealed that elevated PLR was significantly associated with poor OS with a pooled HR of 5.72(95% CI: 3.83-8.56, p<0.001; (Figure 2). In view of the large heterogeneity between the studies (P<0.1, I^2>50%), the random effects model was used.

Considering the possible clinical heterogeneity, we performed subgroup analysis based on the presence or absence of distant metastasis, sample size and PLR cut-off value. As shown in (Figure 3a), according to the presence or absence of distant metastasis, the total HR of the subgroup without distant metastasis was 5.55(95% CI: 3.46-8.91), the HR with distant metastasis was 7.93(95% CI: 2.19-28.71), and the HR with all stages was 5.72(95% CI: 3.83-8.56). The results of the subgroup analysis showed that the increase of PLR was related to OS in the subgroup with or without distant metastasis (HR=5.72,95% CI:3.83~8.56). As shown in (Figure 3b), when subgroup analysis was performed according to the sample size, the sample size <258, HR=5.86(95% CI: 3.32-10.36, P<0.01);PLR≥258 subgroup total HR=5.77(95% CI: 2.81-11.85, P<0.01). As shown in (Figure 3c), when subgroup analysis was performed according to the median of the PLR cut-off value 112.00, the PLR<112 subgroup summary HR=6.34(95%CI:0.92-43.55, P>0.05), PLR≥112 subgroup, HR=5.98(95% CI: 3.60-9.94, P>0.01).

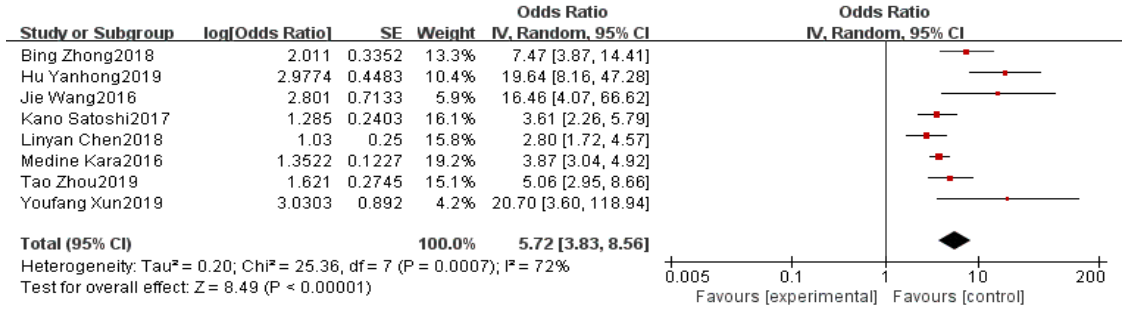

Figure 2: Forrest plot of hazard ratio (HR) for the association of PLR with OS in patients with laryngeal carcinoma.

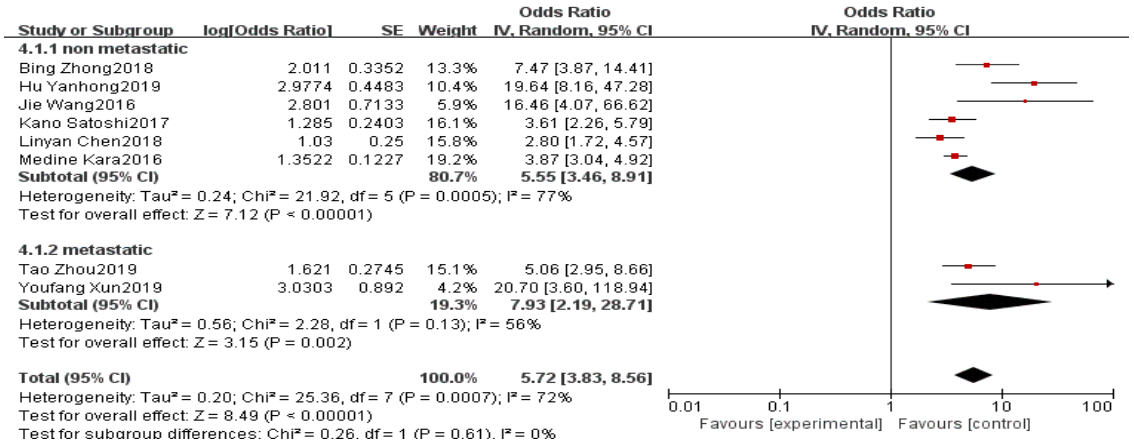

Figure 3a

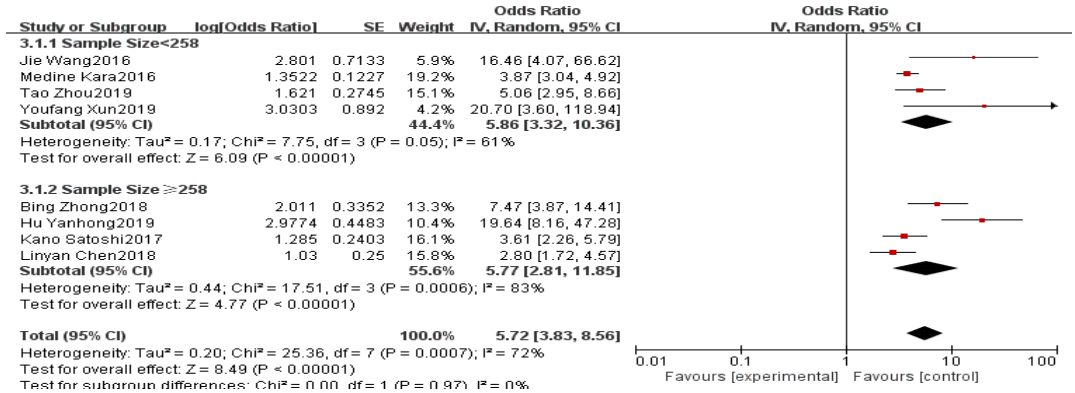

Figure 3b

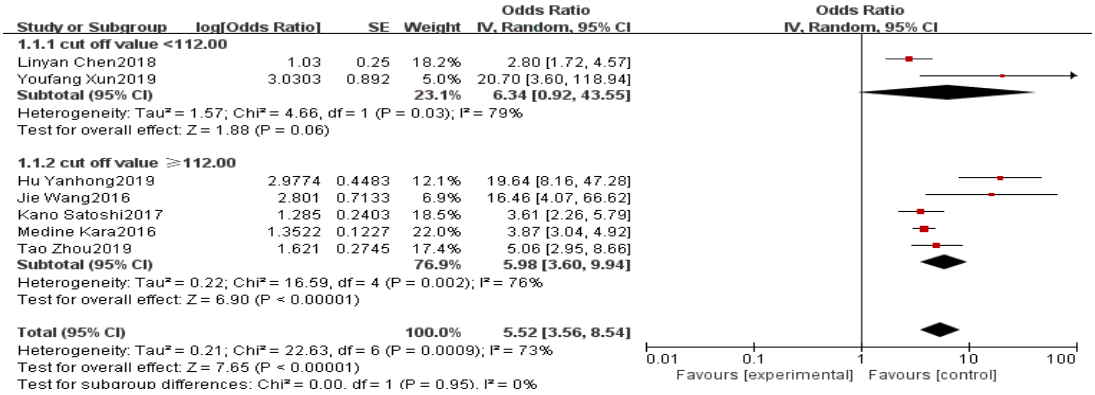

Figure 3c

3.3. Progress-free Survival and Recurrence-free Survival outcomes

There were two studies [12,13] with 512 patients investigated the association between PLR and PFS. The data revealed that elevated PLR was uncorrelated with PFS (HR=22.71, 95% CI: 0.21-2502.48, P>0.05; P<0.1,I^2>50%; (Figure 4). Four studies [14-17] with 1543 patients investigated the association between PLR and RFS. The data revealed that elevated PLR was correlated with shortened RFS (HR=8.06, 95% CI: 5.55-11.70, P<0.01; P>0.1, I^2=0%; (Figure 5).

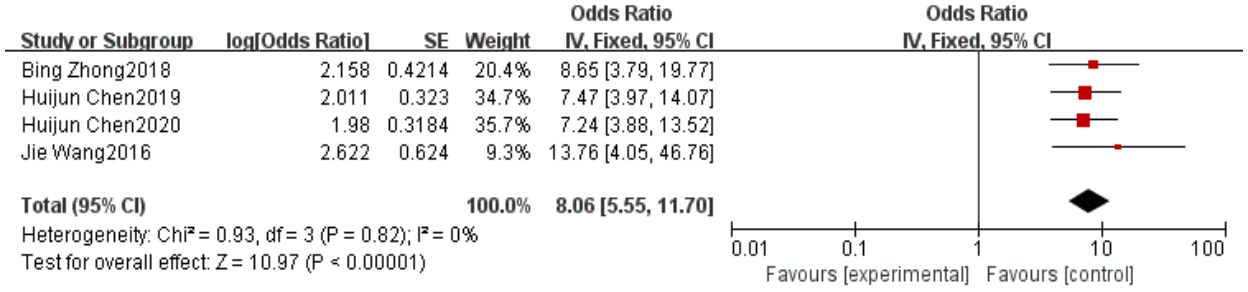

Figure 4: Forrest plot of hazard ratio (HR) for the association of PLR with PFS in patients with laryngeal carcinoma.

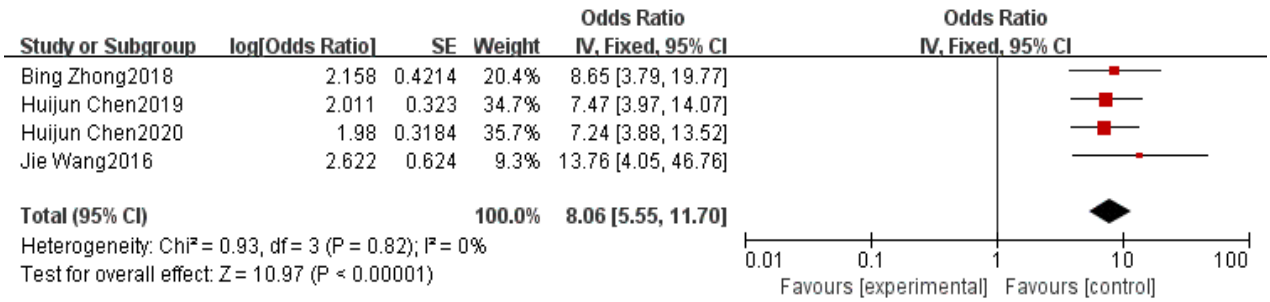

Figure 5: Forrest plot of hazard ratio (HR) for the association of PLR with RFS in patients with laryngeal carcinoma.

3.4. Sensitivity Analysis and Bias Analysis

Each individual study was omitted every time to estimate the influence of individual data sets on the pooled HR. The results showed that the corresponding HRs for OS, PFS and RFS were not markedly changed, indicating the robustness of presented results. Due to the small number of studies included in each result of OS, PFS and RFS, the corresponding funnel plot was not shown.

4. Discussion

In this meta-analysis, we summarized 10 studies [8-17] involving 2961 patients, which investigated the prognostic value of PLR in survival of laryngeal carcinoma patients. The results showed that elevated PLR was associated with poor OS and RFS in patients with laryngeal cancer, but not with PFS. We also performed subgroup analysis, which was stratified according to the presence or absence of distant transfer, sample size and PLR cut-off value. The results showed that the increase of PLR could predict poor OS in the subgroup with or without distant metastasis. The results of stratified subgroup analysis in accordance with the sample size were consistent with the overall analysis results, which further verified the prognostic value of PLR in survival of laryngeal cancer patients, indicating that PLR is a reliable biomarker for the prognosis of laryngeal cancer. However, when stratified by PLR truncation value, PLR cut-off value is only meaningful when ≥112.

Cancer is a complex disease whose outcome depends largely on the cross-talk between the tumor and its microenvironment [18]. Cancer cells, as well as surrounding stromal and inflammatory cells, engage in well-orchestrated reciprocal interactions to form an inflammatory tumor microenvironment (TME) [19]. Platelets and lymphocytes are inflammatory cells that have been extensively studied in the course of tumor development. Platelets are non-nucleated red blood cells with a diameter of 4μm, which have characteristics of multiple functions and short life [20]. Recent years have been ripe with discoveries of non-haemostatic platelet functions. This led to the appreciation of the significant, previously unknown, role played by the platelets in various pathologies and regenerative processes. As a result, exciting opportunities for clinical applications in fields as diverse as regenerative medicine and cancer treatment are emerging [21]. The interaction of tumor cells with platelets is a prerequisite for successful hematogenous metastatic dissemination. Upon tumor cell arrival in the blood, tumor cells immediately activate platelets to form a permissive microenvironment. Platelets protect tumor cells from shear forces and assault of NK cells, recruit myeloid cells by secretion of chemokines, and mediate an arrest of the tumor cell platelet embolus at the vascular wall. Subsequently, platelet-derived growth factors confer a mesenchymal-like phenotype to tumor cells and open the capillary endothelium to expedite extravasation in distant organs. Finally, platelet-secreted growth factors stimulate tumor cell proliferation to micrometastatic foci [22]. In addition, platelets interact with cancer thrombocytes, thereby prolonging the survival of circulating tumor cells and promoting their blocking and adhesion to endothelial cells during metastasis to the site of metastasis. In addition, platelets secrete a large number of tumor, angiogenesis, growth, and permeability factors that regulate tumor growth, epithelial to mesenchymal transformation, and metastasis [20]. Other studies have found that the interaction between tumor cells and platelets produces chimeric extracellular vesicles that promote metastasis through EMT and endothelial activation. IMPs activated endothelial cells and platelets and induced epithelial-to-mesenchymal transition of tumor cells, promoting metastasis [23]. However, T cells are a diverse and important group of lymphocytes that mature and undergo a positive and negative selection processes in the thymus. These cells all play a crucial role in active immunity [24]. It has been reported that the density of tumor infiltrating lymphocytes reflects the anti-tumor immune status [25]. T cell responses are part of the cancer immune cycle and can significantly influence clinical outcomes. In general, the immune system has evolved several mechanisms to protect the host against cancer. Each of them has to be undermined or evaded during cancer development to enable tumor outgrowth [26]. Cytotoxic lymphocytes (CTL) such as CD8+ T and natural killer (NK) cells can recognize and eliminate cancer cells, and thereby restrict the tumor growth and metastasis, if they exert full cytotoxicity [27]. Therefore, tumor-infiltrating immune cells can profoundly influence tumor progression, as well as the success of anti-cancer therapies [28]. Therefore, PLR can represent the balance between pro-tumor response and anti-tumor immune function. More meta-analyses have shown that PLR has prognostic value for a variety of cancers, including non-small cell lung cancer, colorectal cancer, esophageal cancer, pancreatic cancer, etc. The results of this meta-analysis we performed are consistent with previous reports on the prognostic value of PLR and other cancer sites, suggesting that PLR is a promising biomarker for the prognosis of laryngeal cancer. In addition, PLR can be measured in routine blood test in daily clinical practice, which is easy to measure, low cost, good repeatability and strong applicability.

To the best of our knowledge, this is the first time systematically discusses PLR in laryngeal cancer prognosis value of Meta-analysis, summarizes the 10 studies including 2961 patients, the conclusion is convincing, though, the study also has some limitations. In the first place, all the included studies were retrospective studies, selection bias recall bias and other bias may be existed. Secondly, most studies were from China, small number were from Japan and Turkey, thus infer in patients with other regions, should be careful to explain our results. Thirdly, the cut-off value of PLR is inconsistent in various studies, which may lead to heterogeneity. In addition, when summarizing HR for PFS and RFS, only 2 and 4 studies were included, so more studies are needed to support and

supplement.

5. Conclusion

In summary, this meta-analysis confirmed that elevated PLR was associated with poor prognosis in patients with laryngeal cancer. Therefore, PLR is expected to be a biomarker for predicting the prognosis of patients with laryngeal cancer.

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