Prognostic significance of tumor-associated macrophages in patients with nasopharyngeal carcinoma
A meta-analysis
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Abstract
Background: To explore the prognostic value of diverse subsets of tumor-associated macrophages (TAMs) in prognosis in patients with nasopharyngeal carcinoma (NPC) using meta-analyses.

Methods: Relevant studies were searched in the database of PubMed, Web of Science, Embase, Cochrane Library, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang till November 2019. The relationship between TAMs and survival outcomes was estimated by pooling hazard ratios (HRs) and 95% confidence intervals (CIs); and the correlation of TAMs and clinicopathological factors was evaluated by using odds ratios (ORs) and 95%CIs.

Results: Six studies with 1549 patients were included in this meta-analysis. The high expression of CD68+ TAMs was associated with favorable disease-free survival (DFS) (HR = 0.66, 95%CI = 0.50–0.88, P = .005), whereas the density of M2-like TAMs (CD163+, CD68+CCL18+, and CD206+) was correlated to poor overall survival (OS) (HR = 1.77, 95%CI = 1.22–2.56, P = .003) and DFS (HR = 1.96, 95%CI = 1.00–3.85, P = .050) in patients with NPC.

Conclusions: CD68+ TAM density is associated with superior DFS, while CD163+ M2-like TAMs predicted poor prognosis in patients with NPC.

Abbreviations: CCRT = concurrent chemoradiotherapy, CI = confidence interval, CNKI = China National Knowledge Infrastructure, CRC = colorectal cancer, DFS = disease-free survival, EBV = Epstein-Barr virus, HR = hazard ratio, HtrA2 = heat-temperature-required protein A2, IHC = immunochemistry, IT = intratumor, LPS = lipopolysaccharide, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, Oct4 = Octamer-binding transcription factor 4, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PT = peritumor, RT = radiotherapy, TAMs = tumor-associated macrophages, TLR = toll like receptor, TNM = tumor-node-metastasis, TS = tumor stroma.

Keywords: clinical value, meta-analysis, nasopharyngeal carcinoma, prognosis, tumor-associated macrophages

1. Introduction
Nasopharyngeal carcinoma (NPC) is originated from the lining of the nasopharynx and is a rare cancer type, accounting for 0.7% of all new cases and 0.8% of all cancer-related deaths worldwide.[1] It is estimated that about 129,079 new cases and 72,987 deaths are attributed to NPC around the world in 2018.[1] NPC is an endemic cancer in Southeast Asia (especially southern China), where the incidence could be as high as 20 per 100,000 person-years.[2] NPC has a high propensity to distant metastasis among all head and neck cancers. Due to its radiosensitive and chemosensitive behavior and the deep-seated anatomic location, radiotherapy (RT) alone and concurrent chemoradiotherapy (CCRT) are the main treatment methods for NPC.[3] Although Tumor-Node-Metastasis (TNM) staging system and plasma Epstein-Barr virus (EBV) DNA provide important prognostic implications for patients with NPC,[4] the survival outcomes in patients with stage IV disease is poor, with a 5-year survival rate being <10%.[5] Therefore, it is important to identify effective markers that could help in survival prognosis and could also be served as therapeutic targets. The recent advances[6–8] in prognostic markers provided important evidence of clinical use of those indicators. For patients with colorectal cancer (CRC),

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Metadherin mRNA expression is a useful non-invasive biomarker.\[6\] Metadherin mRNA expression is effective for screening and early diagnosis of CRC, and is correlated to advanced tumor stage and a poor prognosis.\[6\] Circulating high-temperature-required protein A2 (HtrA2) mRNA expression was reported as a significant diagnostic marker for breast cancer.\[7\] Decreased serum HtrA2 expression was associated with poor histological grade and advanced TNM stages in breast cancer patients.\[7\] Moreover, Octamer-binding transcription factor 4 (Oct4), which plays a pivotal role in stem cell differentiation and self-renewal, is shown to be connected with progression and prognosis of gastric carcinoma.\[8\] In the tumor microenvironment of NPC, substantial immune cells are infiltrating and consists of the immune microenvironment.

Tumor-associated macrophages (TAMs) are significant components of the tumor microenvironment; and TAMs could also affect the tumor microenvironment, leading to tumor progression.\[9\] TAMs are generally identified by expressing cell surface marker CD68.\[10\] Macrophages can be defined into 2 polarized phenotypes: the “classically activated” M1 macrophages and “alternatively activated” M2 macrophages.\[11\] M1 macrophages can be induced by interferon-γ, lipopolysaccharide (LPS), and toll like receptor (TLR), and express a high level of CD86, CD40, and PD-L1.\[12\] M1 macrophages play pivotal roles in the elimination of pathogens and cancer.\[13\] In contrast, M2 macrophages are generally characterized by the expression of CD163, CD206, CD204 and production of anti-inflammatory factors (IL-10, TGFβ) and chemokines (CCL5, CCL17, CCL18, and CCL22) to facilitate tumor progression.\[13\] TAMs are closely resembling M2 subtype and can constitute up to 80% of tumor content.\[14,15\] Previous studies have explored the prognostic significance of TAMs in patients with NPC, whereas the results are inconsistent due to different TAMs markers (CD68/CD163/CD206) and distinct distribution of TAMs in tumor (intratumor [IT] or peritumor [PT] or both).\[16-21\] For example, some investigators reported TAMs as prognostic factors for poor prognosis,\[16,18\] whereas some other researchers found high density of TAMs were associated with favorable survival outcomes.\[17\] Therefore, we systematically searched relevant studies and performed a comprehensive meta-analysis according to different markers of TAMs in different tumor distribution. In the current meta-analysis, we investigated the difference of survival outcomes between NPC patients with high and low expression of TAMs.

2. Materials and methods

2.1. Literature search

The current meta-analysis was conducted under the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.\[22\] An electronic retrieval was performed in PubMed, Web of Science, Embase, Cochrane Library, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The last search was up to November 2019. The period was from inception to the last search, and the search was conducted by YLC. The search terms were: “tumor-associated macrophage,” “tumor-infiltrating macrophage,” “intratumoral macrophage,” “macrophage,” “nasopharyngeal carcinoma,” “nasopharyngeal cancer,” and “nasopharynx cancer.” The reference lists of the retrieved articles were also carefully examined to identify eligible studies. Because the current study is a meta-analysis and does not involve the collection of samples; therefore, the ethical approval is not required. The various subsets of TAMs in different tissue localization were combined to minimize the heterogeneity among studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria for eligible studies were as follows: the patients were histologically diagnosed with NPC; the expression of TAMs was detected using immunohistochemistry (IHC) method in intratumor (IT) and/or tumor stroma (TS); a cut-off value to stratify high/low TAMs expression was determined; the relationship between TAMs expression and overall survival (OS) and disease-free survival (DFS) was investigated; the hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for survival analysis were reported or sufficient data were given for HRs and 95% CIs calculation;\[23\] full-text studies published in English or Chinese language; there was no limitation to study design. Exclusion criteria were as follows: studies not providing sufficient data for necessary analysis; studies including overlapped patients; case reports, meeting abstracts, reviews, comments, and letters; animal studies. The inclusion and exclusion processes were performed by YLC in accordance with PRISMA guideline.

2.3. Quality assessment

Quality of the included studies was evaluated by the investigator (YLC) using Newcastle-Ottawa Scale (NOS).\[24\] The NOS assessed items consist of 3 parts: selection (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars). Each individual study was scored between 0 and 9; and studies scored ≥6 were considered as high-quality.

2.4. Data extraction

The following information were extracted from the included studies: first author, publication year, country, sample size, patient age, sex, study duration, cut-off value, antibody used for the evaluation, treatment, tumor stage, follow-up, study design, NOS score, HRs and 95% CIs for OS and/or DFS, and clinicopathological factors.

2.5. Statistical analysis

The relationship between TAMs and survival outcomes was estimated by pooling HRs and 95% CIs; and the correlation of TAMs and clinicopathological factors was evaluated by using odds ratios (ORs) and 95% CIs. The heterogeneity among studies was evaluated by using the chi-square-based Q test and I² statistics. In case of significant heterogeneity (I² > 50% or P < .10), a random-effects model was used for analysis. Otherwise, a fixed-effects model was applied for calculation. Sensitivity analysis was performed to assess the stability of the pooled results. Publication bias was analyzed by using Begg funnel plot test. Stata12.0 (Stata Corporation, College Station, TX) software was used for all statistical analysis. A 2-sided P < .05 were considered statistically significant.

3. Results

3.1. Study selection

The detailed screening process was shown in Fig. 1. As shown in Fig. 1, the initial literature search yielded a total of 888 records. After duplicate records were removed, 539 studies remained. By
screening title and abstract, 513 studies were eliminated. A total of 26 studies were evaluated by full-text examination. And 20 studies were discarded due to the following reasons: 19 studies did not provide HRs and 95%CIs for analysis and 1 study included overlapped patients. At last, 6 studies were included in this meta-analysis.[16–21]

3.2. The characteristics of included studies

The main characteristics of included studies are presented in Table 1. The included studies were all from China and used IHC method for TAMs detection. The included studies were published from 1999 to 2018. The total sample size was 1549, ranging from 43 to 580. Four studies marked overall TAMs as CD68(+) [16–18,21] Three studies marked M2-like TAMs as CD163+[19–21] Two studies identified M2-like TAMs as CD68(+)CCL18(+) [18] and CD163(+) [21] All studies detected TAMs expression in intratumor (IT)[16–21] and 2 studies also measured TAMs expression in tumor stroma (TS).[17,19] All 6 studies reported the association between TAMs expression and OS,[16–21] and 5 studies presented the correlation between TAMs and DFS.[17–21] Three studies were published in the English language[18,19,21] and 3 studies were published in the Chinese language.[16,17,20] The NOS scores of the included 6 studies ranged from 6 to 8, which indicated that they were all high-quality studies.

3.3. CD68+ TAMs and OS and DFS

Four studies comprising 1332 cases investigated the association between density of CD68+ TAMs and prognosis in patients with NPC.[16–18,21] There were 4 studies[16–18,21] providing the data on the association of OS and density of CD68+ TAMs in IT. Because significant heterogeneity ($I^2=87.2\%, P<.001$) was detected, a random-effects model was used. The pooled results were HR = 1.05, 95%CI = 0.52–2.10, $P = .890$ (Fig. 2A; Table 2), indicating that high density of CD68+ TAMs in IT had non-significant prognostic value for OS. Two studies[17,21] provided information on the association of DFS and density of CD68+ TAMs in IT. The pooled HR and 95%CI were HR = 0.69, 95%CI = 0.54–0.88, $P = .003$ ($I^2 = 0\%, P = .621$; fixed-effect model; Fig. 2B, Table 2). The data suggested that high density of CD68+ TAMs in IT predicted superior DFS in patients with NPC. One included study[17] provided the data of the relationship of density of CD68+ TAMs in TS and OS and DFS. The data indicated that high expression of CD68+ TAMs in TS was associated with favorable OS (HR = 0.66, 95%CI = 0.49–0.90, $P = .008$) and favorable DFS (HR = 0.66, 95%CI = 0.50–0.88, $P = .005$) in patients with NPC (Table 2).
3.4. CD163+ M2-like TAMs and OS and DFS

TAMs expressing CD163 are identified as M2-like TAMs. Three studies including 369 patients \[19-21\] offered the data on the prognostic value of CD163+ M2-like TAMs in IT on OS and DFS. The pooled data showed that high density of CD163+ M2-like TAMs in IT was correlated to inferior OS (HR = 1.77, 95% CI = 1.22–2.56, \( P = .003\), fixed-effects model; Fig. 2C, Table 2) and inferior DFS (HR = 1.96, 95% CI = 1.00–3.85, \( P = .050\), random-effects model; Fig. 2D, Table 2) in patients with NPC. According to data from one study with 110 patients, high expression of CD163+ M2-like TAMs in TS also predicted worse OS and poor DFS (Table 2) in patients with NPC.

### Table 1

Characteristics of 6 eligible studies in the meta-analysis.

| Author   | Year | Country | Sample size | Sex (M/F) | Study duration | Age mean (range) | Detection method | Marker | Antibody                        |
|----------|------|---------|-------------|-----------|----------------|------------------|----------------|--------|--------------------------------|
| He       | 1999 | China   | 43          | 33/10     | 1985–1990     | 46.8 (22–71)     | IHC             | CD68 (+) | Zhongshan Bio-tech Co Ltd, China |
| Cai      | 2016 | China   | 557         | 416/139   | 2001–2003     | 46 (19–78)       | IHC             | CD68 (+) | NR                              |
| Huang (a) | 2017 | China   | 580         | 446/134   | 2009–2011     | 45 (24–77)       | IHC             | CD68 (+) | CD68: Cat No. sc7083 Santa Cruz, USA |
| Huang (b) | 2017 | China   | 110         | 87/23     | 2008–2012     | NR              | IHC             | CD163 (+) | CD163: Mouse, Abcam, USA         |
| Xia      | 2017 | China   | 107         | 107       | 2009–2010     | 24–77            | IHC             | CD163 (+) | CD163: Mouse, Zhongshan Golden Bridge, Beijing, China |
| Yu       | 2018 | China   | 152         | 121/31    | 1999–2000     | 48 (18–71)       | IHC             | CD163 (+) | CD163: Zhongshan Golden Bridge, China |

| Stage | Treatment | Tissue detection | Cut-off value | Follow-up (month) | Study design | Survival analysis | NOS score |
|-------|-----------|------------------|---------------|-------------------|--------------|-------------------|-----------|
| III   | CCRT      | IT               | >10 cells/field (200X) | 60–120 | Retrospective | OS | 6 |
| I–IV  | Mixed     | IT, TS           | ROC curve     | 2–114 | Retrospective | OS, DFS | 7 |
| I–IV  | Mixed     | IT               | >22 cells/field (400X) | 43 (8–58) | Retrospective | OS, DFS | 7 |
| I–IV  | Mixed     | IT, TS           | Median value  | 53 (10–86) | Retrospective | OS, DFS | 8 |
| I–II  | Surgery   | IT               | >20 cells/field (400X) | To Dec 2015 | Retrospective | OS, DFS | 7 |
| I–IV  | RT        | IT               | >Score 2      | 130 (5–144) | Retrospective | OS, DFS | 7 |

CCRT = concurrent chemoradiotherapy; DFS = disease-free survival; F = female; IHC = immunohistochemistry; IT = intratumor; M = male; NOS = Newcastle-Ottawa Scale; NR = not reported; OS = overall survival; RT = radiotherapy; TS = tumor stroma.

3.4. CD163+ M2-like TAMs and OS and DFS

TAMs expressing CD163 are identified as M2-like TAMs. Three studies including 369 patients \[19-21\] offered the data on the prognostic value of CD163+ M2-like TAMs in IT on OS and DFS. The pooled data showed that high density of CD163+ M2-like TAMs in IT was correlated to inferior OS (HR = 1.77, 95% CI = 1.22–2.56, \( P = .003\), fixed-effects model; Fig. 2C, Table 2) and inferior DFS (HR = 1.96, 95% CI = 1.00–3.85, \( P = .050\), random-effects model; Fig. 2D, Table 2) in patients with NPC. According to data from one study with 110 patients, high expression of CD163+ M2-like TAMs in TS also predicted worse OS and poor DFS (Table 2) in patients with NPC.
3.5. CD68+ and CD68+CCL18+ M2-like TAMs and prognosis

Based on data of one study with 580 subjects,[18] elevated expression of CD68+CCL18+ M2-like TAMs in IT predicted poorer OS (HR = 2.06, 95%CI = 1.35–3.16, P = .001) and inferior DFS (HR = 2.04, 95%CI = 1.37–3.04, P < .001) (Table 2) in patients with NPC. According to a study comprising 107 cases, high density of CD206+ M2-like TAMs in IT was connected to unfavorable OS (HR = 2.96, 95%CI = 1.02–8.60, P = .036) as well as worse DFS (HR = 2.49, 95%CI = 1.08–5.70, P = .025) (Table 2) in patients with NPC.

3.6. Association between TAMs and clinicopathological characteristics of NPC

A total of 5 studies with 1442 patients[16–19,21] investigated the relationship between TAMs and clinicopathological features. The detailed pooled results were shown in Table 3. The combined data suggested that high expression of CD68+ TAMs in IT had non-significant relevance with sex (n = 2, OR = 1.46, 95%CI = 0.80–2.66, P = .223), T stage (n = 2, OR = 1.21, 95%CI = 0.57–2.54, P = .619), or clinical stage (n = 2, OR = 1.31, 95%CI = 0.77–2.21, P = .316) (Table 3).

3.7. Sensitivity analysis

To test the stability of the pooled results, sensitivity analysis was carried out by omitting each eligible study. As shown in Fig. 3A–D, the combined results were not substantially altered by any individual study. Therefore, the results of meta-analysis were reliable.

3.8. Publication Bias

Begg funnel plot was conducted to test potential publication bias. The funnel plots were shown in Fig. 4A–D. The results indicated that there was no significant publication in the current meta-analysis.

4. Discussion

TAMs are an extremely heterogeneous cell population regarding morphology, functions, and tissue location. TAMs also showed different even conflicting prognostic significance for patients with NPC based on relevant studies.[16–21] The results demonstrated that high density of CD68+ TAMs in IT predicted favorable DFS, whereas high density of CD68+ TAMs in TS was a predictor of superior prognosis. Moreover, high density of CD163+ M2-like

| Table 2 |
|---|
| The pooled associations between TAMs subsets and the prognosis of patients with NPC. |

| Subset Location Outcome No. of studies No. of patients HR (95%CI) P Effects model Heterogeneity |
|---|---|---|---|---|---|---|
| CD68+ IT OS 1 1332 1.05 (0.52–2.10) .890 Random 87.2 < .0001 |
| CD68+ DFS 2 709 0.69 (0.54–0.88) .002 Fixed 0.621 |
| CD163+ M2-like IT OS 1 580 2.06 (1.35–3.16) .001 Random 68.4 0.042 |
| CD163+ M2-like DFS 1 557 0.66 (0.50–0.88) .002 – – – |
| CD68+CCL18+ M2-like IT OS 1 709 1.77 (1.22–2.56) .003 Fixed 3 0.357 |
| CD68+CCL18+ M2-like DFS 1 709 1.96 (1.00–3.85) .050 Random 68.4 0.042 |
| CD206+ M2-like IT OS 1 110 2.46 (1.03–5.91) .043 – – – |
| CD206+ M2-like DFS 2 709 3.02 (1.41–6.50) .005 – – – |

DFS = disease-free survival; IT = intratumor; OS = overall survival; TAMs = tumor-associated macrophages; TS = tumor stroma.

| Table 3 |
|---|
| The relationship between TAMs and clinicopathological characteristics. |

| Subset Location Clinical parameters No. of studies No. of patients OR (95%CI) P Effects model Heterogeneity |
|---|---|---|---|---|---|---|
| CD68+ IT Sex (male vs female) 2 709 1.03 (0.73–1.45) .875 Fixed 0 0.876 |
| T stage (T3–T4 vs T1–T2) 3 819 1.01 (0.78–1.32) .935 Fixed 0 0.986 |
| N stage (N1–4 vs N0) 4 1332 1.17 (0.63–2.18) .164 Random 70.8 0.016 |
| Clinical stage (I–II vs III–IV) 3 1289 1.31 (0.86–2.01) .214 Random 52.8 0.120 |
| Distant metastasis/recurrence (yes vs no) 2 1137 1.33 (0.25–7.02) .737 Random 96.7 < .0001 |
| CD163+ M2-like IT Sex (male vs female) 2 262 1.46 (0.80–2.66) .223 Fixed 0.617 |
| T stage (T3–T4 vs T1–T2) 2 262 1.21 (0.57–2.54) .619 Random 54.8 0.137 |
| Clinical stage (I–II vs III–IV) 2 262 1.31 (0.77–2.21) .316 Fixed 19.8 0.264 |

DFS = disease-free survival; OS = overall survival.
TAMs, CD68+ CCL18+ M2-like TAMs, and CD206+ M2-like TAMs were all connected with poor survival outcomes in patients with NPC. However, significant correlation between TAMs and clinicopathological features was not found based on pooled results. Collectively, the present meta-analysis indicated that CD68+ TAMs in IT predicted poor DFS, and high density of various subsets of M2-like TAMs was predictive of inferior prognosis in patients with NPC. To our knowledge, the current study is the first meta-analysis exploring the prognostic significance of TAMs in patients with NPC.

TAMs are a diverse collection of cell types and exert a wide range of biological and pathological roles in tumor environment. CD68 is the most extensively used marker of macrophages and is used to identify overall TAMs. M1 and M2 subsets of TAMs are identified according to polarization. M1 TAMs are known to induce inflammation and play a crucial role in anti-tumor activity. Whereas, M2 TAMs are related to tumor growth, angiogenic, and immuno-suppressive functions. M2 TAMs can also promote tumor cell trans endothelial migration through interaction with tumor cells. Previous meta-analyses also explored the prognostic role of different subsets of TAMs in various cancer types. A recent meta-analysis including 17 studies with 3547 patients suggested that a high density of M2 TAMs in IT was significantly correlated with OS in patients with hepatocellular carcinoma (HCC). Whereas CD68+ TAMs in the IT or TS have no prognostic effects on OS in HCC. Another meta-analysis focusing on TAMs and Non-Hodgkin’s lymphoma (NHL) showed that high-density CD68+ TAMs was associated with poor OS and poor PFS, which suggested that TAMs was a robust predictor of outcomes in NHL. In addition, a recent meta-analysis demonstrated that high stromal expression of CD163+ TAMs correlated with both poor OS and poor DFS in patients with squamous cell carcinoma of the head and neck (SCCHN). However, abundance of CD68+ TAMs was not associated with OS or DFS in SCCHN.

In the present meta-analysis, the results showed the prognostic role of CD68+ TAMs in IT was also not significant for OS in patients with NPC, which was in accordance with the results of SCCHN. Referring relevant meta-analyses on TAMs, I defined TAMs as CD68+ as the overall cell population and CD163+, CD68+CCL18+, and CD206+ as M2-like TAMs. The tissue distribution (IT and/or TS) was used to further stratify the location of diverse subsets of TAMs. The CD68+ TAMs or different subsets of M2-like TAMs in IT or TS are incorporated for meta-analysis, which guarantees the homogeneity of the TAMs subpopulation. In the present meta-analysis, we found the high density of CD68+ TAMs in IT were associated with favorable DFS in NPC, which was in line with the results of TAMs in non-small cell lung cancer (NSCLC). In addition, we identified M2-like TAMs as 3 different cell subpopulations (CD163+, CD68+CCL18+, and CD206+).
pooled data indicated that abundance of all 3 subsets of M2-like TAMs were correlated to poor OS and DFS in patients with NPC. These findings validated the prognostic role of CD163+ M2-like and CD206+ M2-like TAMs in NPC, as the results derived from other cancer types including pancreatic cancer, HCC, esophageal cancer, and bladder cancer. More importantly, for the first time, we reported the significant impact of CD68+CCL18+ M2-like TAMs in meta-analysis. Those results highlighted the potential prognostic and therapeutic value of CD68+CCL18+ M2-like TAMs in patients with NPC. The results of this meta-analysis should be validated in non-Asian patients in clinical trials and open datasets.

Although this is the first meta-analysis focusing on TAMs and prognosis in patients with NPC, there are still several limitations should be acknowledged. First, the sample size was relatively small. Only 6 studies were included, and the data of CD68+CCL18+ M2-like and CD206+ M2-like TAMs on prognosis were extracted from an individual study. Second, all included studies were from China, which may compromise the generalizability of the results to patients in other countries or with other ethnicity. Third, the antibodies to PD-L1 and cut-off values varied in included studies; and the treatment methods were not uniform. Those elements could introduce inherent heterogeneity to this meta-analysis and affect the reliability of results. Fourth, all eligible studies were of retrospective study design, which may increase heterogeneity to this meta-analysis.

5. Conclusions

The presented meta-analysis demonstrated that the high expression of CD68+ TAMs was associated with favorable DFS, whereas the density of M2-like TAMs (CD163+, CD68+CCL18+ and CD206+) was correlated to poor prognosis in patients with NPC. Nevertheless, due to several limitations, further randomized controlled trials recruiting patients from various countries are needed to warrant our results.

Author contributions

Ya-Lian Chen designed the project and performed data extraction and analysis. Ya-Lian Chen performed the quality assessment and drafted the article. Ya-Lian Chen revised the manuscript critically and supervised the project. Author read and approved the final manuscript.

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Figure 4. Publication bias examined by Begg plot test for (A) density of CD68+ TAMs in IT and OS (P = .734); (B) density of CD68+ TAMs in IT and DFS (P = 1); (C) density of CD163+ M2-like TAMs in IT and OS (P = .602); and density of CD163+ M2-like TAMs in IT and DFS (P = 1). CI = confidence interval; DFS = disease-free survival; IT = intratumor; OS = overall survival; TAMs = tumor-associated macrophages.
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