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Review Article

Prognostic significance of tumor-associated macrophages in ovarian cancer: A meta-analysis

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HIGHLIGHTS

- Higher M1/M2 TAMs ratio in ovarian tumors was associated with a favorable OS and PFS.
- High density of CD163+ TAMs might predict poor prognosis in patients with ovarian cancer.
- M1 and M2 subsets presented distinct effects on ovarian cancer prognosis.
- This suggests that M2 subtypes could be a potential therapeutic target of ovarian cancer.
- High density of TAMs was related to advanced TNM stage of ovarian cancer.

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ABSTRACT

Objective. The role of tumor-associated macrophages (TAMs) in tumor microenvironment remains controversial due to the two different polarized subsets of TAMs. Here, we performed a meta-analysis to evaluate the correlation between subpopulations of TAMs and clinical outcomes in patients with ovarian cancer.

Methods. A comprehensive search in PUBMED/Medline and EMBASE databases was performed. The association between TAMs and patient prognosis of ovarian cancer was estimated with hazard ratios (HRs) and their corresponding 95% confidence intervals (95% CIs) using a random-effect model. Additionally, sensitivity analysis and Begg's test were conducted.

Results. Nine studies including 794 patients were enrolled in the meta-analysis. The results showed that higher M1/M2 ratio in tumor tissues was associated with a favorable overall survival (OS) (HR = 0.449, 95% CI = 0.283–0.712, $P = 0.001$). Elevated intra-islet M1/M2 TAMs ratio showed a positive correlation for OS (HR = 0.510, 95% CI = 0.264–0.986, $P = 0.045$). No significant relation was observed between OS and CD68+ TAMs (HR = 0.99, 95% CI = 0.88–1.11, $P = 0.859$), CD163+ TAMs (HR = 1.04, 95% CI = 0.92–1.16, $P = 0.544$) or CD163+/CD68+ TAMs ratio (HR = 1.628, 95% CI = 0.529–5.008, $P = 0.395$). Worse progression-free survival (PFS) was associated with high density of CD163+ TAMs (HR = 2.157, 95% CI = 1.406–3.312, $P = 0.000$) and higher ratio of CD163+/CD68+ TAMs (HR = 3.223, 95% CI = 1.805–5.755, $P = 0.000$). Elevated M1/M2 TAMs ratio predicted better PFS of ovarian cancer (HR = 0.490, 95% CI = 0.270–0.890, $P = 0.019$). Furthermore, high density of CD163+ and CD68+ TAMs was observed in ovarian cancer with advanced TNM stage.

Conclusion. In our study, it was revealed that CD163+ TAMs infiltration was associated with poor prognosis of ovarian cancer and high M1/M2 macrophages ratio in tumor tissues predicted better prognosis.

Contents

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1. Introduction

Ovarian cancer is regarded as one of the most frequent cancer-related deaths in females, with increasing incidence [1]. Despite all current treatment options including surgical resection, chemotherapy, radiotherapy and immunotherapy, patient survival remains poor because of its invasive and metastatic characteristics. Moreover, ovarian cancer is heterogeneous in clinical presentation and its prognosis is therefore affected by various factors, such as tumor stage, grade and histologic subtype [2,3]. The proliferation and invasion of cancers is mediated by various mechanisms including immune cells within tumor microenvironment. Intense research is imperative to investigate the association between the expression of immunologic biomarkers and patient survival of ovarian cancer, and it has been identified that intraepithelial tumor-infiltrating T cells strongly predicted better outcomes of ovarian cancer [1].

A number of studies have focused on the roles of macrophages within tumor tissues which constitute a major population of innate myeloid cells, named as tumor-associated macrophages (TAMs). Immature monocytic precursors from bone marrow circulate in the blood stream, and are then recruited into tumor sites where they differentiate into different phenotypes in response to different environment stimuli: the classically activated type M1 and the alternative activated type M2 [4,5]. Subtypes are distinguished by surface markers and play divergent roles in tumor growth [6]. Interferon-γ and tumor necrosis factor (TNF)-α induce TAMs into M1 macrophages, which mediate inflammatory response and present antitumor activity [7]. M2 macrophages are mainly activated by interleukin 4 (IL-4) or interleukin 13 (IL-13) and promote tumor development through multiple mechanisms [8].

Because of the heterogeneity of TAMs subsets, the role of TAMs in local tumor microenvironment remains controversial. The prognostic value of TAMs has been recently discussed in breast cancer [9], lung cancer [10], prostate cancer [11], liver cancer [12] and gastric cancer [13]. Numerous publications suggested that TAMs benefited tumor growth and were therefore associated with worse outcomes [13,14]. However, several studies held the opposite view that high density of macrophages were correlated with longer survival [15–17]. With regard to the roles of TAMs in ovarian cancer, various biomarkers including CD68, CD163 and HLA-DR were used to identify different types of TAMs and the microdistribution of TAMs in tumor islet or tumor stroma was also widely discussed [18,19]. Previous studies reported different prognostic effects of TAMs on ovarian cancer depending on TAMs subtypes and the distribution of TAMs in tumor tissues. Here, we performed a meta-analysis to evaluate the correlation between subpopulations of TAMs and clinical outcomes in patients with ovarian cancer.

2. Methods

2.1. Search strategy

We performed a comprehensive search in PUBMED/Medline and EMBASE databases to identify all relevant studies published before March 2017 on the prognostic value of TAMs in patients with ovarian cancer. The following search terms were used: “tumor-associated macrophages OR TAMs” and “prognosis OR prognostic OR survival OR outcome” and “ovarian cancer OR ovarian tumor OR ovarian carcinoma OR ovarian neoplasm”. Titles and abstracts were checked to identify potential eligible articles, and then full texts were reviewed. Also the references of included articles were checked manually for more relevant studies. The meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20].

2.2. Inclusion and exclusion criteria

The study was included in this meta-analysis if meeting the following inclusion criteria: (1) published in English, (2) investigating patients with ovarian cancer, (3) containing the information of TAMs expression, and (4) evaluating the correlation between TAMs level and survival outcomes of patients with ovarian cancer. Articles were excluded if meeting any of the following exclusion criteria: (1) not providing enough information to estimate HRs and 95% CIs; and (2) reporting duplicate or overlapping data.

2.3. Data extraction

Two authors independently extracted the required data from all enrolled studies. The following information was extracted: the first author's name, publication year, country, number of patients, cut-off value, survival analysis, the HRs of TAMs for OS and PFS, histologic subtypes of ovarian cancer, specimens processing, biomarkers of macrophage phenotypes. If the HRs and 95% CIs could not be acquired directly, they were estimated from Kaplan-Meier curves using the method described by Parmar et al. [21]. All disagreements were settled by a face-to-face consultation with a third author.

2.4. Statistical analysis

The association between TAMs and the prognosis of patients with ovarian cancer was estimated by synthesis of all available HRs and the corresponding 95% CIs according to Tierney's method [22]. Cochran's Q test and Higgin's I^2 statistics were used to evaluate the heterogeneity of pooled HRs [23,24]. P value < 0.05 and/or I^2 > 50% indicated potential

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