INPLASY PROTOCOL

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None declared.

Prognostic value of podoplanin in various tumors

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Review question / Objective: **The prognostic significance of podoplanin (PDPN) in tumor cells for cancer patients' survival remains controversial. Therefore, we performed this meta-analysis to clarify the relationship between the podoplanin-positive tumor cells and cancer prognosis.**
Eligibility criteria: **The studies were excluded when they met the following criteria: (1) They were published as letters, case reports, reviews and conference abstracts, and in non-English languages. (2) Studies did not provide enough information to extract the data. (3) Studies detected podoplanin density not in tumor cells, or metastatic tissues. (4) Duplicate publications.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 June 2021 and was last updated on 29 June 2021 (registration number INPLASY202160113).

INTRODUCTION

Review question / Objective: **The prognostic significance of podoplanin (PDPN) in tumor cells for cancer patients' survival remains controversial. Therefore, we performed this meta-analysis to clarify the relationship between the podoplanin-positive tumor cells and cancer prognosis.**

Condition being studied: **Podoplanin, a sialomucin-like type 1 transmembrane glycoprotein, also known as GP36, GP40, Aggrus, T1A, has been found in a variety of normal tissues, including glomerular podocytes, lymphatic endothelial cells, heart, type I alveolar cells, and skeletal muscle. Podoplanin plays a crucial role in cell motility, organ development, lymphangiogenesis, blood-lymph separation, platelet production, and immune response. However, its physiological functions are still largely unknown. In pathology conditions, a**

growing body of evidence indicates that it plays an important role in tumorigenesis. There is evidence that podoplanin correlates with tumor-associated lymphangiogenesis and cancer-associated fibroblasts (CAFs). High expression of podoplanin has been observed in various kinds of tumor cells, such as oral cancer, esophageal cancer, lung cancer, cervical cancer, renal cancer, and cutaneous basal cell carcinoma. However, the function of podoplanin remains controversial in tumor cells. In most kinds of cancers, the podoplanin expression is associated with a higher carcinoma cell migration , leading to cancer metastasis, lower survival rates, and poor tumor stage. On the other hand, some studies suggest that podoplanin expression is a protective factor in lung and lip carcinoma. Thus it is an important subject that needs to be further explored.

METHODS

Participant or population: Patients with cancer.

Intervention: Positive or negative expression of podopalnin in tumor cells.

Comparator: Podoplanin expression in tumor cells.

Study designs to be included: The studies were included in this meta-analysis when they met the following criteria: (1) Studies were published as original research articles. (2) The density of podoplanin was evaluated in human tissues. (3) They obtained the density of podoplanin+ tumor cells by histological or pathological examinations. (4) They provided hazard ratios (HRs) or odds ratios (ORs) with 95% confidence interval (CI), or Kaplan – Meier curves of high and low podoplanin+ tumor cells density with OS, and/or DFS

Eligibility criteria: The studies were excluded when they met the following criteria: (1) They were published as letters, case reports, reviews and conference abstracts, and in non-English languages. (2) Studies did not provide enough information to extract the data. (3) Studies detected podoplanin density not in tumor cells, or metastatic tissues. (4) Duplicate publications.

Information sources: We searched Pubmed and EBSCO websites to obtain the density of podoplanin in solid tumors and the survival in patients up to August 2019. The citation lists of the studies we searched were also used to identify other eligible studies.

Main outcome(s): The present study involved 2155 patients from 21 eligible studies. Data from these studies revealed that high expression of podoplanin was associated with a poor survival rate in cancer patients. To determine the prognostic value of podoplanin in different cancers, we conducted stratified analyses by tumor types. The results showed that podoplanin-positive tumor cell infiltration had a negative prognostic effect associated with survival in esophageal cancer and oropharyngeal cancer. However, no relationship between podoplanin expression and survival was observed in other tumor-type patients. The results show a difference between OS and DFS. The reason for this discrepancy may be due to the limited number of eligible studies including DFS data, in which changes of some included studies could influence the pooled data. In addition, high expression of podoplanin in tumor cells was significantly associated with N stage, T stage, TNM stage and vascular invasion. No significant correlations were found with age, gender, tumor size, lymph node status, and tumor differentiation. These results provide meaningful evidence that the expression of podoplanin in tumor cells is a negative prognostic marker in esophageal cancer and oropharyngeal carcinoma. For such patients with high podoplanin expression in esophageal and oropharyngeal tumor cells, close follow-up is necessary. And targeting podoplanin is a new direction for cancer drug development.

Quality assessment / Risk of bias analysis: The quality of included studies was assessed by The Newcastle–Ottawa Scale

(NOS). Two independent authors provided the NOS score and achieved consensus. A score ≥ 6 denoted a high quality. Sensitivity analysis, Begg funnel plot, and Egger test were performed to assess the influence of individual study and the publication bias.

Strategy of data synthesis: If the included studies showed the HRs and 95%CI in text or tables, we extracted it directly. Otherwise, we calculated the HRs and 95%CI from Kaplan–Meier curves via Engauge Digitizer version 4.1. Then, we combined extracted data into meta-analyses with STATA.

Subgroup analysis: The stratified analyses were implemented based on cancer type.

Sensitivity analysis: Sensitivity analysis, Begg funnel plot, and Egger test were performed to assess the influence of individual study and the publication bias.

Language: English.

Country(ies) involved: China, Japan, South Korea.

Keywords: podoplanin; prognostic value; cancer; meta-analysis.

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