NY-ESO-1 expression in solid tumors predicts prognosis
A systematic review and meta-analysis

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Abstract

Background: New York esophageal squamous cell carcinoma 1 (NY-ESO-1) is a member of the cancer testis antigen family. NY-ESO-1 has documented potential as an effective target for cancer immunotherapy. The prognostic value of NY-ESO-1 expression in solid tumors, however, remains controversial because of inconclusive data.

Methods: For this analysis, the Medline, Embase, and Cochrane Library databases were searched up to February 2018 for studies investigating NY-ESO-1 expression in solid tumors and overall survival (OS), progression-free survival (PFS), or disease-free survival (DFS). Hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted from each study. Pooled HRs and CIs were calculated using the Mantel-Haenszel fixed effects or random effects model.

Results: A total of 23 studies were included in the analysis. The combined HR (95% CI) estimates for OS, PFS, and DFS were 1.41 (95% CI: 1.24–1.61; I² = 0%), 1.62 (95% CI: 1.42–1.84; I² = 17%), and 0.95 (95% CI: 0.86–1.59; I² = 57%), respectively.

Conclusions: NY-ESO-1 expression in solid tumors is associated with worse OS and PFS. Studies are still needed to provide more evidence.

Keywords: meta-analysis, New York esophageal squamous cell carcinoma 1, solid tumor, survival

1. Introduction

New York esophageal squamous cell carcinoma 1 (NY-ESO-1) is a protein consisting of 180 amino acids, and its gene is located in the Xq28 region of the X chromosome. As a member of the cancer testis antigen (CTA) family, NY-ESO-1 has been shown to be expressed in spermatogonia, primary spermatocytes, oogonia, and placenta and in a variety of cancers, such as melanoma, ovarian cancer, cervical cancer, etc.[1,2] The blood-testis barrier makes the testis an immune privileged organ. In view of this property, NY-ESO-1 is believed to be a promising target for cancer immunotherapy, and it has been widely researched since its discovery. Accumulating evidence indicates that NY-ESO-1 is one of the most immunogenic antigens in the tumor-associated antigen family.[1] Therefore, multiple clinical trials with variable results have been carried out to advance the bedside application of NY-ESO-1-based cancer immunotherapy.[3-6]

Unlike the unambiguous immunogenicity of NY-ESO-1, the prognostic relevance of its expression in solid tumors, however, remains controversial. Varied survival outcomes have been reported in studies focused on the prognostic value of NY-ESO-1 expression. Therefore, we conducted the first comprehensive meta-analysis of published literature on this topic to summarize the evidence.
2.2. **Inclusion criteria**

In order to be eligible, studies had to discuss the relevance of NY-ESO-1 expression to survival and provide sufficient data for extracting or estimating the hazard ratio (HR) and 95% confidence interval (CI).

2.3. **Exclusion criteria**

Studies were excluded from the analysis if the articles were not written in English, the articles were reviews or letters, the studies did not investigate solid tumors, or primary data could not be extracted or used to calculate essential information for the meta-analysis.

2.4. **Data extraction**

The primary data were the HR and 95% CI of survival outcomes [overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS)]. OS: the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. PFS: the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. DFS: the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. Three reviewers (HW, DC, and Wen Quan) independently extracted the primary data and baseline characteristics from the included studies. Only Kaplan-Meier survival curves, not the HR and 95% CI, were provided in some included articles. For these articles, methods based on the work of Parmar et al,[7] Williamson et al,[8] and Tierney et al[9] were used to calculate the HR. The baseline characteristics included the first author, publication year, tumor type, study size, methods to detect NY-ESO-1 expression, percentage of patients with positive NY-ESO-1 expression, and HR estimation methods. Disagreements were resolved by discussion.

2.5. **Statistical methods**

The logHR and standard error were calculated using software designed by Matthew Sydes and Jayne Tierney (Medical Research Council Clinical Trials Unit, London, UK).[9] The pooled HR was obtained using fixed or random effects models depending on the presence of heterogeneity among studies. Heterogeneity was evaluated with Cochran Q test and the $I^2$ index and was defined as $P < .10$ or $I^2 > 50%$.[10] Forrest plots showed the pooled HR. HR > 1 indicated worse survival outcomes. Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies. Funnel plot, Begg test, and Egger test were conducted to predict the publication bias. All calculations were conducted using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and Stata Software 11.0 (Stata, College Station, TX).

As a validation, we also used www.kmplot.com Web site to explore the relationship between the expression of NY-ESO-1 mRNA and prognosis. Data of this Web site were based on TCGA database.

3. **Results**

3.1. **Characteristics of eligible studies**

A total of 134 articles were obtained from the literature search. After the title and abstract were read and the full text was reviewed, 23 studies were included (Fig. 1).[11–33] Eligible studies investigated synovial sarcoma, melanoma, adenoid cystic carcinoma of the head and neck, ovarian cancer, breast cancer, non–small cell lung cancer (NSCLC), head and neck squamous...
3.2. NY-ESO-1 expression and overall survival

Twenty-one of the 23 included studies evaluated the association of NY-ESO-1 expression with OS. The HR and 95% CI were provided in 4 studies enrolling patients with breast cancer or NSCLC [14, 18, 20, 30]. In the other studies, the HR and 95% CI were extracted from the given Kaplan-Meier survival curves. A fixed effects model was used, and the pooled HR (positive vs negative) was 1.41 (95% CI: 1.24–1.61; I^2 = 0%, P = .54; Fig. 2A). The results showed increased mortality among solid tumor patients with positive NY-ESO-1 expression. The funnel plot showed no obvious publication bias (Fig. 3A). The Begg test (P = .778) and Egger test (P = .389) also revealed no significant publication bias.

3.3. NY-ESO-1 expression and progression-free survival

Five of the included studies investigated PFS [11, 13, 21, 22, 27]. Four of these studies directly reported the HR and 95% CI [11, 14, 20, 22]. Survival data for the other studies were acquired using the method developed by Matthew Sydes and Jayne Tierney. HRs (positive vs negative) of PFS were pooled by a fixed effects model (Fig. 2B). The results (pooled HR: 1.62; 95% CI: 1.42–1.84; I^2 = 17%, P = .31) demonstrated that positive NY-ESO-1 expression in tumor tissue indicated worse PFS. No obvious publication bias was found in the funnel plot (Fig. 3B). The Begg test (P = .806) and Egger test (P = .515) showed no significant publication bias.

3.4. NY-ESO-1 expression and disease-free survival

Four of the included studies investigated DFS [14, 20, 24, 33]. In contrast to the OS and PFS results, the pooled HR for DFS was 0.95 (95% CI: 0.86–1.19; I^2 = 0%, P = .21), which indicated a nonstatistically significant trend of the beneficial effect of NY-ESO-1 expression (Fig. 2C). The funnel plot (Fig. 3C), Begg test (P = .308) and Egger test (P = .211) found no significant publication bias.

3.5. NY-ESO-1 mRNA level and OS

We searched the Web site www.kmplot.com and the analysis based on TCGA database in this Web revealed that high level NY-ESO-1 mRNA predicted poor prognosis in lung adenocarcinoma patients [HR 2.67, 95% CI (1.31–5.44), P = .005].
4. Discussion

As far as we know, this is the first meta-analysis discussed the prognostic value of NY-ESO-1 expression. Heterogeneity exists in NY-ESO-1 expression among different histological types of tumors. The highest NY-ESO-1 expression rate was previously reported as up to 82% in neuroblastoma.[34] In the present article, the included studies used either immunohistochemistry or Quantitative Real-time PCR to detect NY-ESO-1 expression, and the expression rate ranged from 4.3% (head and neck squamous cell carcinoma)[16] to 67.8% (vulvar cancer).[27] Five included studies on the same cancer type (NSCLC) showed different expression rates, ranging from 10.0% to 24.8%, among patients,[15,17–18,25,30] similar to the varied result which is reported by another study.[2] As a subgroup, we analyzed the OS predictive value of NY-ESO-1 expression in NSCLC patients. The pooled HR (positive vs negative) was 1.48 (95% CI: 1.14–1.92; $I^2=43\%$, $P=.14$), which also revealed a worse outcome in NY-ESO-1-positive NSCLC patients. Consistently, the analysis of kmplot.com Web site data also suggests that high level NY-ESO-1 mRNA is associated with poor prognosis. Heterogeneity in NY-ESO-1 expression in a certain tumor type may be due to detection methodology. Immunohistochemical methods have adopted different antibodies against certain epitopes of NY-ESO-1, such as E978, ES121, B.9.8.1.1, and D8.38. In addition, Laban et al.[16] discussed NY-ESO-1 protein localization in their study. The survival outcomes of the cytoplasmic and nuclear co-expression group and the cytoplasmic or nuclear-only expression groups were compared to those of the negative expression group, and a statistically significant shorter OS was discovered in the co-expression group. The present study, however, pooled the HRs of only the single location (nuclear or cytoplasmic) expression group to minimize heterogeneity among the included articles. Cochran Q test ($P=.54/31$) and the $I^2$ index ($I^2=0\%/17\%$) for the pooled analysis of OS/PFS showed that the heterogeneity among the included studies was acceptable. For the pooled analysis of DFS, the Q test ($P=.07$) and $I^2$ index ($I^2=57\%$)
tended to indicate that random effects models should be used to calculate the pooled HR.

The correlation of NY-ESO-1 expression and survival may be caused by the biological function of NY-ESO-1 in cancer cells, which has not been fully elucidated. According to the specific expression in spermatagonia and primary spermatocytes and the lack of expression in differentiated spermatids in the testis, it is speculated that NY-ESO-1 may play a role in germ cell self-renewal or differentiation.\[^{[35]}\] In terms of cancer cells, a specific interaction has been discovered between NY-ESO-1 and another CTA, melanoma antigen gene C1 (MAGE-C1), which is believed to play a role in cell cycle progression and apoptosis.\[^{[36,37]}\]

In addition, NY-ESO-1 expression in mesenchymal stem cells (MSCs) has been documented by immunofluorescence analysis of bone marrow cells.\[^{[38]}\] Cancer stem cells (CSCs) are similar to MSCs and possess self-renewal ability and differentiation potential, which are closely related to therapeutic resistance in cancer. Through a study on CSCs isolated from glioma cell lines and tissues, Yawata et al.\[^{[39]}\] found stronger and more frequent expression of NY-ESO-1 in CSCs than in differentiated cells. This evidence may partially explain the increased mortality and worse PFS of patients with NY-ESO-1-positive solid tumors. The opposite result for DFS may be attributed to the relatively small sample size enrolled. Therefore, the biological function of NY-ESO-1 in cancer cells and the prognostic value of NY-ESO-1 expression still need to be further investigated.

Limitations of the present meta-analysis need to be discussed. First, the HR and 95% CI of some included studies were extracted, and log(HR) and se(log(HR)) were then calculated by software provided by Matthew Sydes and Jayne Tierney. Potential biases may relate to this process. Second, only 23 studies met the inclusion criteria, and these studies investigated 13 different types of cancer. In the future, more studies could be added to our meta-analysis to validate the present results, and subgroup analysis should be conducted according to tumor type. Finally, our meta-analysis used only published data. Updated individual patient data were not obtained; if those data were added to our analysis, the accuracy and validity could be improved.

In conclusion, our meta-analysis suggests that NY-ESO-1 expression in solid tumors has prognostic value. Positive NY-ESO-1 expression could predict shorter OS and PFS. No significant prediction ability for DFS was found. More high-quality studies are eagerly needed to elucidate the biological function of NY-ESO-1 and to provide more evidence of its prognostic value.

**Author contributions**

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